

VOLUME 4 *New York Number* NUMBER 5

THE
MEDICAL CLINICS
OF
NORTH AMERICA

MARCH, 1921

PHILADELPHIA AND LONDON
W. B. SAUNDERS COMPANY

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PUBLISHED SIX MONTHS (SIX NUMBERS A YEAR) BY W. B. SAUNDERS COMPANY, WEST WASHINGTON
SQUARE, PHILADELPHIA
PRINTED IN AMERICA

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THE MEDICAL CLINICS OF NORTH AMERICA

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NUMBER 5

CLINIC OF DR WARFIELD T LONGCOPE

PRESBYTERIAN HOSPITAL

JAUNDICE FOLLOWING THE ADMINISTRATION OF ARSPHENAMIN

THIS afternoon I wish to show you 3 patients, all of whom present evidence of a disease which has run a uniform course in each of the individuals. They present a problem which it will be well worth our while to consider in some detail.

CASE I

The first patient, C O, history No 48,557, a carpenter by trade, was admitted to the hospital December 31, 1920, complaining of jaundice, which he had had for twelve days. Though he was born in Louisiana, he has lived in the northern part of the United States for thirty-four years. His work has not exposed him to contact with any of the heavy metals. Until quite recently he has been a very heavy drinker. He has always been vigorous and healthy, though in his youth he had pneumonia and during the epidemic last year influenza. He denies having contracted any venereal disease.

Five months ago he was admitted to the hospital with the following symptoms: drowsiness, weakness, and dizziness, which had been increasing over a period of six months. The examination then showed very definite drowsiness, some slowing of the mental processes, but no other abnormalities which could be detected in examination of the nervous system. The prostate was enlarged and the radial arteries were thickened. It was at

first suspected that he might have lethargic encephalitis, but a lumbar puncture disclosed a spinal fluid with 44 cells, a ++++ Wassermann reaction, and a paretic curve in the colloidal gold solution. He was immediately given antisyphilitic treatment, and during his stay in the hospital received 13 grams of mercury bichlorid intramuscularly and a total of 4.95 grams of arsphenamin intravenously in eight doses. Before he left the hospital he was given one intraspinal treatment and was finally discharged April 24th greatly improved. He was referred to the Out-patient Department for further treatment, and during the summer received seven intravenous injections of arsphenamin of 0.3 gram, making a total of 3.1 grams, and 3 grams of mercury salicylate. In all, then, he has had about 7 grams of neo-arsphenamin and arsphenamin, the last dose being administered October 19, 1920. He did extraordinarily well, gained 27 pounds in weight, and up to his recent illness had returned, for all practical purposes, to normal health.

Nine days before he was admitted, when he felt quite well, a barber told the patient that he was yellow. Since that time the yellow color has steadily increased. During this period the patient's appetite has been poor, he has had a bad taste in his mouth. He vomited once, seven days after the onset of jaundice, and the stools have become light in color. He has had no fever, no chills, and no abdominal pain.

The patient, as you see, is very deeply jaundiced and is of a dark yellowish-green color. The pupils react sluggishly to light, are equal but somewhat irregular. Only a few teeth remain and there is pyorrhea about them. Examination of the chest shows no abnormalities. The abdomen, as you may see in the epigastric region, is somewhat protuberant, and on palpitation the entire epigastrium and almost the complete right side of the abdomen is filled by a smooth mass taking the form of the liver, which has a palpable margin and extends well below the umbilicus and 13 cm. below the costal margin in the right mammillary line. In this region there is a deep notch. The spleen is not palpable, the Achilles' jerks are both absent. During his stay in the hospital his temperature has varied between

98.2° and 99.8° F, his pulse between 64 and 78, and his respirations have been normal. The blood count shows 75 per cent

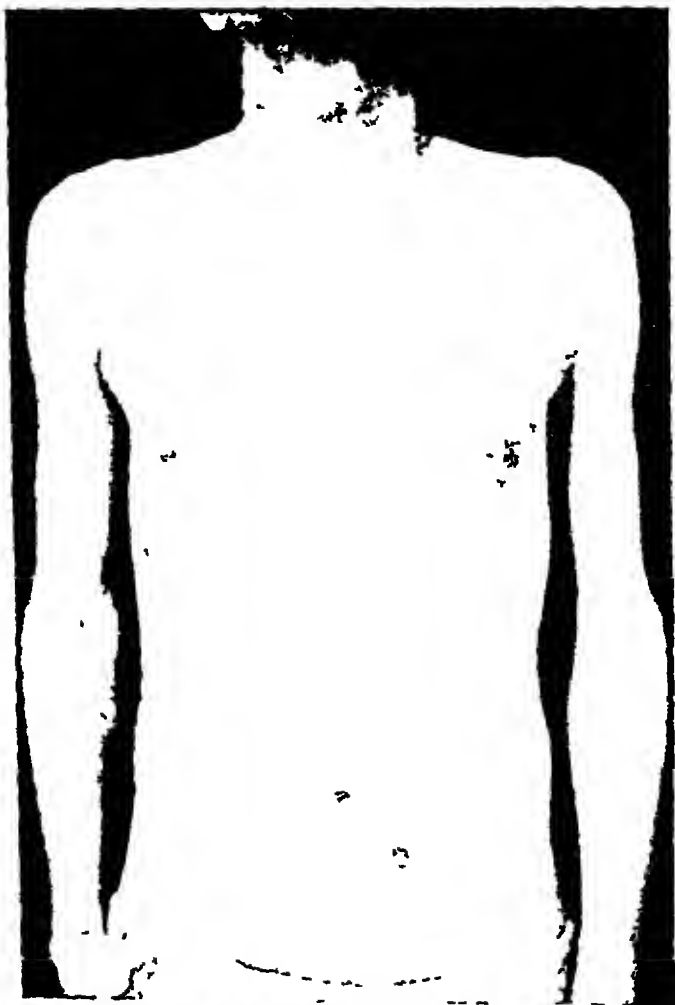


Fig. 129—Case I, showing the extent of the liver enlargement on admission to the hospital and the reduction in the size of the liver shortly after admission.

hemoglobin, red blood-cells 4,880,000, 7800 white blood-cells, polymorphonuclears 73 per cent, lymphocytes 25 per cent,

basophils 2 per cent The urine has been dark, the specific gravity 1021, and it has shown faint traces of albumin and large quantities of bile

Shortly after his admission it was noticed that the liver began to diminish in size, and by January 3d, though the jaundice, if anything, was deeper, the liver only reached $4\frac{1}{2}$ cm below the costal margin in the right mammillary line (Fig 129) At this time the stools were light greenish in color, semiformed, and did not contain bile The blood Wassermann was ++++ in both antigens, blood sugar 0.95 gram per liter, blood urea 0.25 gram per liter, the blood fat was 0.74 per cent, blood uric acid 2.2 mg per 100 c c, and blood cholesterol 0.2 per cent

On January 4th a duodenal tube was passed and a yellow, slightly viscid fluid returned in spurts through the tube Examination of this fluid showed that the protein, fat, and starch-splitting ferments were present in normal concentration Though the fluid looked as though it contained bile, reaction to Smith's reagent was negative On the same day, however, estimation of the urobilin content of the stool showed that urobilin was present in 800 dilution units—very small amounts On January 13th gastric expression obtained by the serial method gave the following results

	One-half hour	One hour	One and a half hours	Two hours
Free hydrochloric acid	0	30	24	28
Total acid	20	50	64	48

On January 15th, for the first time, the stools were a light brown, semiformed, and gave a reaction for bile

x-Ray of the stomach has shown that it empties in six hours, that there is no deformity within this organ or in the duodenum By January 20th the patient had definitely improved, the color of the skin had lightened, and the feces showed urobilin and urobilinogen in 13,000 dilution units x-Ray of the gall-bladder region did not show any shadows that suggested gall-stones

Though many of the features of this case suggest that the jaundice is due to temporary obstruction, there are others, such as the rapid decrease in the size of the liver during the period

of obstruction, which speak strongly against it. Any permanent obstruction due to such causes as new growth can be excluded, and we could only consider such causes as stone or catarrhal jaundice. The association of this jaundice with arspenamm treatment is of such importance that it must be considered seriously as the etiologic agent ¹

CASE II

This patient, P J, history No 48,733, is a married woman thirty years of age, who was admitted to the hospital January 15, 1921, complaining of indigestion, nausea, constipation, and jaundice of about three weeks' duration. She is an Austrian who came to this country ten years ago. Her father died many years ago at the age of twenty-eight of what was suspected to be tuberculosis, and she has one brother said to be insane. She has been married eleven years. Her first child died of diphtheria at the age of two years. She has two daughters, five and seven years of age, both alive and well. She has done housework and washing and helped to support the family. Until a few years ago she was quite healthy, though she had scarlet fever in childhood and typhoid eight years ago. In the autumn of 1918 she had influenza. Until the attack of influenza, except for the two previous illnesses she had been quite healthy.

Influenza occurred in October, 1918, from which she recovered slowly, and finally, in January, 1919, she came to the Dispensary of the Presbyterian Hospital complaining of "dizziness and headaches." She was also nauseated and occasionally vomited. She complained of rather vague pains in various portions of her body which came on particularly after her washing. She has not used alcohol.

In January 1919 the general examination showed some caries of the teeth but nothing else of much significance. The blood-pressure was 120/75. She returned to the dispensary on several occasions for treatment but did not seem to improve.

¹Since this patient was presented, he has steadily improved, and the liver is diminishing still further in size and the jaundice is rapidly clearing up. At the same time bile is present in large quantities in the feces.

After several visits it was learned that she had contracted a primary lesion from her husband three years previously, and a Wassermann reaction done May 24, 1920 showed ++++ in both alcoholic and cholesterol antigens. Examination at this time failed to disclose any evidence of organic disease, but she was immediately placed on antisyphilitic treatment. Between June 15th and October 7, 1920 she was given six injections of salicylate of mercury in 1-grain doses and arsphenamin injections as follows: July 8th, 0.2 gram, July 15th, 0.2 gram, July 22d, 0.3 gram, September 2d, 0.3 gram, September 9th, 0.3 gram, September 23d, 0.3 gram, September 30th, 0.3 gram, October 7th, 0.3 gram. During this period her headaches improved.

For four weeks previous to her admission to the hospital, on January 15, 1921, she had had anorexia, some epigastric pains, eructations of gas, and occasional sensations of nausea. She was constipated and her bowels moved only by catharsis. There was no vomiting. Eight days before admission she noticed that the skin of the chest appeared yellow, and this jaundice rapidly spread all over the body. There has been very little itching. Weakness has appeared, some malaise, and the anorexia has increased. The epigastric pain has disappeared, and yesterday, for the first time, the patient vomited. She has noticed recently that the stools have been white. There has been no fever.

Physical Examination—As you can see by the chart, the temperature, pulse, and respiration on admission were normal and have remained so during her stay in the hospital. The temperature has ranged from 98.2° to 99.8° F, and the pulse from 74 to 84. The respirations have varied from 18 to 20.

The physical examination today shows practically the same condition as was found on admission. The jaundice, as you can see, is of an intense grade and is deep orange or greenish-yellow in color. The patient appears somewhat undernourished, but is perfectly comfortable and complains of no pain. There are a few acne pustules over the chest and back. The teeth are poor and some show cavities, while others are missing. Examination of the lungs and heart show no abnormalities. The

blood-pressure is 105/65 The abdomen varies much in its appearance On some days, particularly in the lower portion, there is tympanitic distention, and on others immediately after an enema or catharsis the abdomen is soft and rather flat At these times there is no resistance and the abdomen can be palpated with great ease Under these circumstances it is possible to feel a mass in the left hypochondrium, which presents a rounded edge, comes just below the costal margin, and takes the form of the spleen The margin of the liver can readily be felt as a palpable, insensitive edge Below it, in the midclavicular line, a rather firm, rounded mass, somewhat larger than an egg, can frequently be readily palpated, and as you can see today, when the hand is placed in the right lumbar region and pushed forward, a shadow is seen on deep respiration in the region near this mass The mass can be pushed forward, becoming superficial It is not tender and there has been some dispute as to whether, at the height of inspiration and at the time when it descends lowest in the abdomen, it can be held after expiration in the same position Discussion has arisen as to whether this mass is a dilated gall-bladder or a movable and palpable right kidney Further examination of the patient showed that the hemoglobin is 75 per cent, red blood-cells 5,200,000, white blood-cells 11,200, polymorphonuclears 64 per cent, small mononuclears 27 per cent, large mononuclears and transitionals 6 per cent, eosinophils 3 per cent The smear shows no abnormal cells

The urine shows a specific gravity of 1015, is acid, greenish yellow, and albumin and glucose are absent Microscopically, there are no casts Large quantities of bile are present The stool is pale gray, rather fluid, and to Smith's reagent gives a negative test for bile Though the urine contains large quantities of bile, on January 18th there was no urobilin present

The picture, therefore, so far presents the appearance of a rapidly progressive jaundice accompanied by slight enlargement of liver and spleen and possibly of the gall-bladder, and presents all the appearances of jaundice caused by obstruction to the

common bile-duct On January 18th the stools were examined for urobilin and traces of this substance were found

Formerly we were dependent largely upon the examination of the stools for information concerning the potency of the bile-ducts and the secretion from the pancreas and from the liver, but now, by the use of the duodenal tube and by lavage of the duodenum with magnesium sulphate, a technic first suggested by Dr Meltzer and recently practised by Dr Lyon, of Philadelphia, to produce relaxation of the sphincter of the papilla of Vater, it is possible to obtain bile not only from the common duct, but from the gall-bladder and hepatic ducts, and to identify the bile as coming from these regions An attempt was therefore made to determine whether by lavage of the duodenum with magnesium sulphate the obstruction could be temporarily relieved and by this method bile obtained This test was made on January 22d The duodenal contents obtained by lavage with magnesium sulphate was watery, alkaline, and though definitely tinged green, gave no test for bile with Smith's reagent The appropriate tests, however, showed that this material contained all of the pancreatic fluids in fairly high concentration After flushing the duodenum with magnesium sulphate a viscous fluid which was more deeply tinged with green came through the tube in several separate gushes, but after eight or ten gushes began to flow very slowly Only a few cubic centimeters could be obtained in a period of twenty minutes After the removal of the bile the duodenum was flushed with magnesium sulphate and the tube withdrawn None of this greenish material gave positive tests for bile with Smith's reagent But this test gives information only as regards the presence of bilirubin and not biliverdin, and it is possible that the latter and not the former was present in the material The stools obtained on January 22d, the day following the first lavage, and again on January 26th, following a second duodenal lavage with magnesium sulphate, appeared for the first time brown, and though they gave no reaction with Smith's reagent, on the 24th the dilution units of urobilin had increased greatly, so that they numbered, according to Dr Bauman, who has been

studying this patient, 4800 On January 20th an x-ray of the gall-bladder region showed a shadow, according to Dr Imboden, which was below the liver and which suggested to him a large gall-bladder It seems obvious, therefore, that though there are many signs that suggest obstruction of the common duct, this cannot be complete, or in the first place the ferments of the pancreatic juice in the duodenum seem normal in concentration, which would be distinctly against obstruction at the papilla of Vater, and even before duodenal lavage small quantities of bile pigments did reach the duodenum

After flushing with magnesium sulphate the quantities of bile pigments were greatly increased and were sufficient to color the stools and to appear in readily measurable units of urobilin in the feces

CASE III

This patient, C K, history No 48,797, age fifty-nine years, married, was sent into the hospital for observation on account of an attack of jaundice which has been of somewhat long duration and has lasted now for a period of four months For the last two weeks he has had a dull persistent ache in the upper right quadrant of the abdomen There is a history of tuberculosis in the family His mother died of pulmonary tuberculosis at the age of thirty-five years and two brothers have both died of the same disease at the ages of twenty-three and thirty-three Three sisters have likewise died, two of tuberculosis, one at the age of twenty-three and the other at twenty-eight During the illnesses of his brothers and sisters this patient was living in the same house He has been married thirteen years, his wife is fifty-seven years of age, and is not well, for she had a paralytic stroke twenty years ago There have been no children and no miscarriages He has never been very robust, though the only serious malady from which he has suffered was a severe attack of rheumatic fever in 1889 and a milder attack in 1899 At the age of fifteen he had a very severe sore throat and since then he has been subject to mild sore throats For the last few years he has occasionally had palpitation and has on rare occasions noticed a slight pain about the heart

In 1902 he contracted syphilis. About seven years ago he was told that he had heart trouble. Several months ago he went to the Vanderbilt Clinic for treatment and had there nine injections of arsphenamin. These were administered at weekly intervals between July 31st and September 15, 1920. The treatment was then discontinued on account of the pain in the upper right quadrant of the abdomen. About October 12th, he noticed jaundice, and following this for a short time he spent part of each day in bed. The jaundice at first deepened and then gradually cleared, until at the present time, as you see it has almost disappeared.

The patient on admission looked well nourished and quite well preserved for fifty-nine years of age. He walked into the hospital. The scleræ and the skin showed a very slight degree of jaundice. The pupils were irregular and unequal, the left being larger than the right, and they reacted neither to light nor accommodation. The ophthalmoscopic examination showed pulsating retinal vessels. There was a distinct tremor of the lips and the voice was husky. In the neck there were marked arterial pulsations which could be seen. Over the precordial area a visible and palpable heave was noted with a suggestion of a thrill at the base. The cardiac impulse was seen and felt $11\frac{1}{2}$ cm from the midline in the fifth space. On percussion the cardiac dulness was distinctly enlarged with a wide area of dulness in the first and second spaces, reaching at least 5 cm to the right, and in the first space $5\frac{1}{2}$ cm to the left, while in the second space it was 7 cm to the left. On auscultation, loud systolic and diastolic murmurs were heard all over the cardiac area. The pulse now is 84 and collapsing in quality. The blood-pressure is 190/58. Capillary pulses were seen in the fingers and pistol-shot sounds heard in the groin. On rectal examination, the prostate was found enlarged. The neurologic examination showed no further abnormalities of reflexes or sensation. It was, however, suspected that there was not only syphilitic aortitis, but aortic insufficiency. The blood Wassermann was + + + +. Lumbar puncture showed clear fluid with 25 cells per cubic centimeter. Globulin + + +, and both alco-

holic and cholesterin Wassermann ++++ in quantities of from 2 to 0.2 c c of spinal fluid

It is obvious that we have in this patient again the subject of syphilis with involvement of the aorta and the nervous system, the appearance of jaundice following a moderate source of intravenous injections of arsphenamin. He differs from the other two cases inasmuch as we see him during the recovery from his jaundice. Neither the spleen nor the liver is palpable on examination. The urine was 1025, alkaline, rather dark, glucose and albumin were absent, and the sediment consisted of amorphous phosphates.

Examination of the duodenal contents in this man showed a golden yellow fluid which contained all the pancreatic ferments and bile. After lavage with 20 c c of 20 per cent sterile magnesium sulphate a rapid flow of yellow cloudy fluid was obtained, which was followed in two minutes by clear yellow fluid.

The chemistry of the blood was as follows: Blood fat 0.80 per cent, blood cholesterol, 0.22 per cent, blood uric acid, 2.6 mgm per 100 c c, blood urea, 0.35 gram per liter, showing a normal proportion of these substances. Since admission to the hospital the patient has had no fever, his pulse has varied between 70 and 80, and he has continued to improve rapidly.

These 3 patients present a condition which has not infrequently been observed to follow the administration of arsphenamin in syphilitics and which forms one group representative of the untoward effects that arise during this form of treatment. These by-effects are quite numerous, but we are particularly interested now in those where the liver itself is involved.

Do you, Mr ———, know what other types of intoxication may result from treatment by arsphenamin in syphilitic disease of the liver?

STUDENT I believe that in certain cases of syphilis of the liver, where the syphilitic lesion is quite extensive, treatment by arsphenamin is supposed, by the destruction of the spirochetes, to allow of the liberation of toxic substances which give rise to serious symptoms.

DR LONGCOPE Do you know how these reactions have been designated and where else they may occur?

STUDENT I believe they have been termed Herxheimer reactions and may show themselves especially by a return of the skin lesion or by symptoms referable particularly to the cranial nerves in cerebrospinal syphilis

DR LONGCOPE Yes, the Herxheimer reaction represents probably one type which is to be differentiated from the condition in the patients whom we have just seen Is there anything in the examination of these patients that would make you hesitate to infer that the condition is produced solely by the action of some toxic substance upon the liver cells?

STUDENT Certainly the first and second patients showed many of the features of an obstructive jaundice

DR LONGCOPE Yes, though we know from the subsequent course which the jaundice has taken in these patients that it has not been caused by a permanent or an irremediable obstruction of the bile-ducts, yet it is extremely difficult to eliminate a temporary obstruction as a cause of the condition It would be desirable, however, before coming to any definite conclusion, for us to study to a certain extent the observations that have already been made upon arsphenamin jaundice and to determine whether the patients which we have just seen conform to the descriptions that have been given of this type of jaundice

Before, however, discussing this type of jaundice in detail, it might be well to consider in general the most important causes of jaundice and their classification Into what general groups have cases of jaundice been usually divided?

STUDENT First, jaundice due to obstruction, second, jaundice due to infections or intoxications, third, congenital jaundice

DR LONGCOPE The divisions which you have given are generally recognized by most authors, and I have placed on the board this outline which you will see

TABLE I—CAUSES OF JAUNDICE

- I Obstruction
 - II Infections and intoxications (with and without changes in the liver)
 - (a) Pneumonia Streptococcus infections, malaria, etc. Cardiac disease (chronic passive congestion)
 - (b) Infections of liver
 - 1 Spirochetoses
 - Yellow fever (*Leptospira icteroides*)
 - Acute infectious jaundice (*Spirochæta icthæmorrhagica*)
 - Syphilis (*Spirochæta pallida*)
 - 2 Due to other organisms (cholangitis due to *Bacillus coli*, etc.)
 - (c) Intoxications or infections of unknown origin
 - Acute yellow atrophy
 - Epidemic jaundice
 - (d) Chemical poisons of known origin (causing necrosis of liver)
 - Phosphorus
 - Chloroform
 - Arsenic
 - Toluenediamin
 - Tetrachlorid of ethane tetrachlorethane ("dope" waterproofing aëroplanes)
 - Trinitrotoluol (T N T)
 - (e) Snake venom
 - Dinitrobenzene, picric acid (used in manufacture of explosives)
 - Arsenuretted hydrogen
 - Paroxysmal hemoglobinuria
 - Blood transfusions
- III Congenital
 - Hemolytic icterus
 - Congenital icterus of newborn

} Associated with marked blood destruction

The obstructive jaundice we need not consider at the present moment. Though the so-called congenital jaundice is usually placed in a separate group, some of these cases have the characteristics of those tabulated under the jaundice produced by infections and intoxications, namely, those listed in Group II.

Let us concentrate upon the second group, namely, jaundice due to infections and intoxications. As Willcox (Lancet, 1919, Vol I, page 869) has recently pointed out, jaundice in this second group may or may not be associated on the one hand with destructive changes in the liver, or on the other with destruction of the red blood-cells (hematohepatogenous). As you

may see, I have divided the jaundice produced by infections and intoxications in a somewhat arbitrary manner into (a) general bacterial or protozoal infections, such as pneumonia and malaria, etc., and as a subdivision the jaundice of cardiac disease which, though dependent upon destruction of the liver cells, is often associated with streptococcus infections, under (b) the group of highly interesting spirochetal infections, two of which are so characteristically accompanied by jaundice, under (c) the intoxication and infections of unknown origin, and under (d) the chemical poisons which produce in a large proportion of instances destruction of liver tissue, but some of which may also cause a hemolysis of blood cells, and under (e) are those intoxications which produce, par excellence, the destruction of red blood-cells and are fundamentally hemolytic in nature

Information concerning the toxic action of many of the chemicals grouped under *d* and *e* has come about through the use of such chemicals during the manufacture of explosives and munitions during the war. Some of the most recent information concerning the action of these substances can be obtained from Colonel Willcox's article

The subgroups in this list which interest us particularly are the spirochetal infections of the liver and the chemical poisonings which are associated with necrosis of the liver, for in the cases which I have presented to you there are at least two features to be considered. First, late syphilitic infection, and the other, the use of arsenic. During what stages of the disease may jaundice occur in syphilis?

STUDENT I believe that it is observed during the florid stage of the disease. Second, as an acute necrotic hepatitis, and third, as a result of compression of the bile-ducts by gummata or an extensive syphilitic cirrhosis.

DR LONGCOPE The last of these possibilities does not probably come into consideration today, and we are particularly interested in those types of jaundice which are unassociated with the ordinary forms of duct obstruction. Recently this entire subject of jaundice in syphilis has been discussed by

Scott and Pearson in the American Journal of Syphilis, 1919, Vol III, page 628, and they divide the jaundice of syphilis which is not produced by obstruction into three types (a) Jaundice due to diffuse syphilitic hepatitis, (b) jaundice accompanying a diffuse syphilitic hepatitis in which the symptoms are to be ascribed to the destructive action by the first injections of arsenical preparations upon the spirochetes, namely, a jaundice possibly appearing as the result of the Herxheimer reaction, to which you have already referred, and (c) the early and late arsenical jaundice to which they think those cases of syphilis are particularly susceptible in which the liver is already infected by the *Spirochæta pallida*

Concerning the cause of this latter type of jaundice there has been much discussion, which is set forth in this article of Scott and Pearson, for some observers have held that the jaundice, after repeated administration of arsphenamin, is dependent largely upon the action of the substance upon the spirochetes infecting the liver, while others ascribe it entirely to arsenical poisoning. These represent the extreme points of view, while many observers, such as Scott and Pearson, take an intermediate ground and consider that both factors are operative.

Recently this entire subject has been discussed quite extensively in several articles, and the information derived from reports of isolated cases of jaundice following arsphenamin treatment has been amplified by observations upon much longer series of cases. This useful paper of L. W. Harrison in the Quarterly Journal of Medicine, 1917, Vol X, page 291, gives an excellent summary of the untoward effects which have been observed after the use of arsphenamin, and he describes jaundice as occurring in 0.6 per cent of the cases which he has treated. His experience is very large and comprises 10,000 cases under treatment by salvarsan and mercury. He describes the condition very briefly as simulating obstructive jaundice and states that in one case which had died with an extensive dermatitis the liver showed no changes but that the common duct where it entered the duodenum was inflamed and obstructed. He, as well as all other observers, has noted that the jaundice

occurs almost exclusively in those patients that have had repeated injections. In a more recent article in the Archives of Internal Medicine for 1920, Vol 26, page 521, which was published November 15th, Stokes, Ruddeman, and Lemon discuss this entire question of jaundice during syphilitic treatment and its possible relationship to infectious jaundice. They state that from August, 1916 to July, 1920 5200 patients were treated by arsphenamin at the Mayo Clinic, and during this period 70 cases of jaundice, excluding those definitely associated with carcinoma of the liver, have been observed. They also quote Meirowsky's experiences, who reports among 225,780 injections of arsphenamin, neo-arsphenamin, and arsphenamin sodium that jaundice occurred once in each 2000 injections of arsphenamin, or 0.89 per cent, and once in 6000 injections of neo-arsphenamin.

You can see by these figures that the condition is not very rare, and since a number of fatal cases have been reported, it has a very important significance. Apparently there is no way at the present time of foretelling whether or not jaundice is likely to occur after treatment, nor is it possible to determine at what time the jaundice may occur after the series of treatments has been completed. You will note that in 3 of these cases a considerable time elapsed after the last administration of arsphenamin and the appearance of jaundice, and this has been noted not infrequently in the reported cases. In many instances the jaundice does not appear for several weeks after the administration of the last dose of arsphenamin.

The cases which you have seen present in many ways very good illustrations of this condition which frequently runs its course over periods of weeks, accompanied by few symptoms except for the jaundice. There may or may not be in the early stages enlargement of the liver, and the condition observed in the carpenter, fifty-five years old, in which the liver on admission was of enormous size and rapidly diminished, is undoubtedly unusual. One feature which presented itself in 2 of these cases is the great diminution of bile-pigments in the feces, and though this has been observed, it is of unusual occurrence, and, as a rule, the feces throughout the course of the disease

contain large quantities of bile-pigments. The blood chemistry of these patients has not shown any remarkable alterations except for the presence of bile-pigments in the plasma. Bailey and McKay (*Archives of Internal Medicine*, 1920, Vol. 25, page 628), in their study of a series of such cases which came under their observation in No. 16, Canadian General Hospital, at Orpington, Kent, state that the blood uric acid and the blood sugar of these patients is normal, but that the blood urea is slightly elevated. The high urea values, they think, may be accounted for by the increased protein consumption of their patients for long periods previous to their examinations.

In the fatal cases death apparently takes place with much the same symptoms as are observed in acute yellow atrophy. The pathology of this condition has been described now in quite a number of fatal cases but since the pathologic picture seems to vary somewhat we have not as yet anything like complete information concerning this important part of the study. In most of the single reports more or less extensive destruction of the liver cells has been described but perhaps one of the most complete studies is that made by H. M. Turnbull, of the London Hospital, whose report upon the examination of tissues from 8 cases of death following injections of salvarsan appeared in the 55th Special Report Series of the Medical Research Committee for 1920. He states that the liver in all cases was the seat of a destructive lesion which was remarkably uniform in the different cases. The centers of the lobules seem to have been most vulnerable. There is degeneration and necrosis of some cells, with fatty deposits in other cells. Where the necrosis has been most rapid (usually about the center of the lobule) the fat is least prominent, while it is greatest in the cells which survive the longest. Thus, the fatty cells are more likely to be found about the margins of the lobules than in the center, where the necrosis proceeds most rapidly. In some instances there is to be seen fibroblastic proliferation about the portal system or central veins. In these regions cellular infiltration is present and of an early type, containing many leukocytes. In some cases where the necrosis and degeneration have ad-

vanced further in one region than another, regeneration of liver cells was observed. In none of these cases were there bacteria or spirochetes found. No accumulation of bile-pigments were found in the sections of the liver. In one other organ, namely, the kidney, there is quite extensive fatty degeneration which affects as well the heart muscle. Cholangitis was frequent and hemorrhages into the intestines and into the tubules of the kidneys occurred in some instances. Turnbull concludes that the pathologic alterations which he observed in these cases and which are well illustrated in these plates that I will project upon the screen are not those which are ordinarily met with in infections of the liver by spirochetes, but bear a strong resemblance to those changes which have been attributed to exogenous poisons. Though they resemble somewhat the pathologic lesions produced by phosphorus poison, they simulate much more closely the changes observed after poisoning by trinitrotoluol and tetrachlorethane.

From the pathologic picture, therefore, one is inclined to uphold the view that the jaundice in these cases is the direct result of arsenical poisoning. So far, however, according to Bailey and McKay, arsenic has not been found in the urine of these patients, and Lynch and Hoge, who have reported in the *Journal of the American Medical Association*, 1919, Vol 73, page 1687, 3 cases of this type of poisoning, 1 of which was fatal, confirm this observation, and state that even in the tissue of the fatal case which was subjected to various tests, arsenic could not be demonstrated. They point to the fact that the stools may be pasty or of light color, and give a negative test for bile.

At the present moment, therefore, we cannot be absolutely certain that arsenic is the cause of the necrosis, though there seems to be considerable evidence which points in this direction.

Before referring for a moment to one important question in the prevention and therapy of these conditions, I may refer again to the difficulty of diagnosis which may arise, and remind you that Stokes, Ruddeman, and Lemon seemed to feel quite

definitely that the recent frequent occurrence of jaundice following arsphenamin at Rochester is due to the fact that many of these patients suffered from an intercurrent disease which was entirely unassociated with either syphilis or the mode of treatment. They call attention to the fact that during the period in which jaundice increased in instance among the patients receiving arsphenamin there was in that region a sufficient number of cases of jaundice among non-syphilitics and untreated individuals to constitute an epidemic, and they conclude that many of their patients were suffering from an epidemic form of jaundice and not the type which they recognize as incidental in a certain number of cases, to arsphenamin treatment.

There is one other point which I desire to bring forward, namely, the possible prevention of this condition during arsphenamin treatment. It has been shown by Opie and Alford, *Journal of the American Medical Association*, 1914, Vol 62, page 295, that the liver of animals is least likely to be damaged by chloroform and phosphorus if the diet is high in carbohydrates, while Graham (*Journal of Experimental Medicine*, 1915, Vol 21, page 185) has demonstrated that in dogs the resistance of the liver to chloroform is proportional to the amount of glycogen in that organ. In more recent experiments Davis and Whipple (in the *Archives of Internal Medicine*, 1919, Vol 23, page 612) investigated this subject still further, and from experiments on dogs poisoned by chloroform have concluded that in starvation injury to the liver is to be expected. Sugar and diets rich in carbohydrates fed in the days preceding chloroform anesthesia exert a marked protective action against liver injury. Thus a diet of skimmed milk alone is highly protective and a diet of bread and skimmed milk or any food rich in carbohydrate gives the largest liver repair whereas fat diets do not aid in the liver repair.

We have therefore, in the patients that you have seen reduced the fat of the diet to a minimum and have placed them on a relatively high carbohydrate intake. Whether this has had any influence on the course of the affection or not it is

difficult to say, but at least in the 2 patients whom we have seen early in their disease the course has been generally mild and the recovery comparatively rapid

In summary, therefore, I think we are justified in stating that these patients present many of the characteristics of jaundice in syphilis following arsphenamin intoxication, and though there are certain features which may be raised as argument against this diagnosis, still the study of this condition has not yet been so fully completed that the slight irregularities justify us in changing our opinions concerning them. It has not been possible to add anything further to the important subject of the exact etiology, and we must still be left in doubt as to whether the condition is produced entirely by arsenical poisoning or by the combined action of arsenic and its effect upon the syphilitic liver. There seems, however, to be sufficient evidence to conclude for the present that the arsenic intoxication is an important feature, and we have therefore instituted the only treatment which may theoretically be of benefit, namely, a high carbohydrate diet, and which, if it has not resulted in cure, at least has been accompanied by improvement in 2 of these cases

CLINIC OF DR T STUART HART

PRESBYTERIAN HOSPITAL

THE FUNCTIONAL ACTIVITY OF THE HEART. METHOD OF CLASSIFICATION

THIS afternoon, gentlemen, I wish to direct your attention to the subject of the *classification* of patients with heart disease

Hitherto most of your time spent in the examination of the heart has been given over to a study of the anatomic conditions. You have perfected yourselves in the several methods which have for their object the detection of abnormalities in the valves of the heart, so that you are able to say with a good deal of assurance as to whether the mitral or the aortic or the tricuspid valves are or are not anatomically perfect, and if imperfect, you can usually determine whether the anatomic changes form an obstruction to the blood-stream or permit the blood to leak backward in a direction opposite to the normal. You can detect changes in the pericardium and are able to state in one case that this sac is bulging with fluid, in another that its cavity is obliterated and its walls glued together by adhesions.

While these anatomic facts are of importance to the clinician they are so only to the degree in which they effect the work of the heart, or in which they may in the future be expected to affect its work.

The subject to which I specially wish to invite your attention is the *functional activity of the heart*, that is to say, What is the work which the heart performs and how does it perform it?

Before we can intelligently consider abnormalities of heart function we must, for the sake of comparison, formulate standards based on the normal heart. We may therefore inquire, What is the function of the normal heart? What is the work we may expect the normal heart to do?

The function of the heart is to maintain an adequate circulation in all of the organs of the body. A sufficient quantity of blood must be supplied to each organ so that everywhere the tissue respiration may be satisfactorily performed. The heart must act as an efficient pump which keeps the blood effectively moving through the vessels of the greater and lesser circuits. It is the great motor power which, supplemented by other agencies (*e g*, muscle contractions, valves of the veins, respiratory movements of the chest, etc), keeps the blood circulating so that all parts of the organism may receive a sufficient supply.

The circulation must be adequate not only for periods when the organs are relatively inactive but also for periods when under stress they are called upon to increase their activities to a high degree. When the body is at rest the normal heart liberates only a small portion of the force of which it is capable, the power which is available under conditions of bodily activity is known as the "reserve force." This factor of safety is very considerable. Lowy has estimated that the reserve force of the heart enables it to perform thirteen times the amount of work which is demanded of it when the body is at rest. A moderate increase of bodily work calls for a quadrupling of the work of the heart, but a normal heart will readily perform this task year after year if its work is alternated with proper intervals of rest.

For practical purposes it is extremely useful to employ some method of classification which takes into consideration both the anatomic condition and functional capacity of the heart.

I have placed on the blackboard the classification which is at present used in this clinic.

CLASSIFICATION OF HEART DISEASE

Class I—Organic heart disease—which has never given symptoms of cardiac insufficiency

Class II—Organic heart disease—with symptoms of cardiac insufficiency in the past, none at the present time

Class III—Organic heart disease—with symptoms, at the time of examination, of cardiac insufficiency following ordinary exertion

Class IV—Possible heart disease—presenting abnormal physical signs the nature of which leads us to believe that they are not due to organic changes in the heart

Class V—Potential heart disease—those in whom there is no evidence that the heart is damaged, but who are suffering from any infectious condition which may be accompanied by a diseased heart, *e g* , syphilis, rheumatism, tonsillitis, chorea, etc

This classification was adopted several years ago by the Associated Cardiac Clinics of New York City. It is not a perfect one. It is difficult to arrange one suited to all tastes. It is, however, simple, workable, and has the advantage of making the grouping of cases uniform in a large number of institutions. The classification has received the endorsement of the Association for the Prevention and Relief of Heart Diseases and I commend it to you for every-day use. Some day you may be in the position to point out a better method of grouping, but the best way to prepare yourself for this is to use this classification and thus discover its possible defects.

I wish to present for your consideration today a rather large number of patients for one session. I do this for the reason that I want you to fix your attention on the great variation in the functional capacities of these hearts and to compare them one with another, so that the object of a grouping made on the basis of this classification may be clear. As we proceed I think it will become evident to you that our advice to the patient as to his methods of living and the kind of occupation which he should select is in a large measure determined by the functional capacity of the heart, this classification helps us in that it indicates the capacity of a group of individuals.

In order to bring before you so many patients it will be necessary to abbreviate their histories, but I shall try to give you the important points in each one, omitting details having no direct bearing on the question at present under consideration.

Case I—Mitral Stenosis. No Cardiac Insufficiency.—The first patient who is presented today is a lawyer thirty-two years of age who came to see me last week and has kindly volunteered to come before you today. He came complaining that he had

been refused as an acceptable risk by a life insurance company ten days previously on account of a valvular defect of the heart, he had never been aware of anything abnormal and could not believe that anything was wrong with his heart

He says that he has never been ill but once in his life, an attack of severe dysentery ten years ago, the acute symptoms lasted two weeks and were followed by jaundice, but he completely recovered, and since then has been perfectly well He has never had rheumatism, gonorrhea, syphilis, or any other infection He uses alcohol and tobacco in moderate amounts, never to excess He has always been very athletic, in his college days he played football on the Varsity team and was a "shot-putter" of some repute He has always been fond of wrestling and boxing and has followed these forms of exercise up to the present time Less than a month ago he fought an exhibition match of five rounds with a well-known pugilist

He has never been conscious of his heart, he has never been unduly short of breath, has had no cough, no symptoms referable to the digestive or genito-urinary tracts, no edema

I will ask two of you to make a brief physical examination to corroborate my findings

He is a well-put-up man of good color Pulse of good volume and quality, regular, no thickening of the arterial walls Heart-apex palpable in the fifth space at the midclavicular line, here there is felt a short fine thrill which precedes the apex-thrust, which is sharp and tapping On percussion there is no evidence of enlargement of the heart On auscultation there is heard at the apex a short presystolic rumble terminating in a snapping first sound The second sounds at the base are both distinct, the second pulmonic is very loud and accentuated The heart rate is 68 Blood-pressure, systolic 130 mm Hg, diastolic, 85 mm Hg The remainder of the physical examination shows nothing abnormal At my office a few days ago I put him through a series of pretty lively exercises He showed no shortness of breath, no change in color, no distress The heart increased in rate to 110, but returned to 70 after two minutes' rest, immediately after exercise the presystolic thrill

and rumble were increased in intensity. It is clear that this man has a mitral stenosis, and it is equally clear that he has no cardiac insufficiency. He still has a large reserve. Since he shows evidence of organic disease of the heart without any functional incapacity we must assign him to Class I. He was justly refused a life insurance policy by a company which accepts no one with definite organic disease of the heart, and yet if he follows advice he bids fair to outlive his expectancy.

You notice that this patient has an unusually slow pulse for one showing a well-marked mitral stenosis. I believe this is one reason that accounts for the continued efficiency of the heart under the strains to which he has subjected it.

We commonly think of the heart as an "unresting" organ, but this view is quite an improper one. The heart works during systole and rests during diastole. In a normal heart, beating at a rate of 70, the cardiac cycle occupies 0.862 second. In such a heart Edgren has estimated that the duration of systole is 0.379 second, diastole 0.483 second, and that the time occupied by diastole in a twenty-four-hour period is, therefore, over thirteen hours. In the accelerated heart the shortening of the cycle is almost entirely at the expense of the diastole period, the length of systole remaining practically unchanged. In a heart beating 140 per minute the total time occupied by diastole in twenty-four hours is reduced to less than four hours. It is, therefore, quite evident that a reasonable heart rate must be an important factor in preserving its efficiency.

We shall advise this man to give up his more strenuous forms of exercise, but not to lead a sedentary life; he should take moderate exercise regularly, live a clean, hygienic life, and avoid infections. I think he would be playing more safely to cut out the use of alcohol and tobacco altogether. There is no drug that will help his present condition.

Case II—Aortic Insufficiency. Auricular Fibrillation. No Cardiac Insufficiency at the Present Time.—This young woman is thirty-six years of age, single, and supports herself by sewing. When she first came to the hospital two years ago she told us that when she was eighteen years of age she had a severe attack

of rheumatic fever, after being in bed with severely inflamed joints of both legs and both arms for four weeks she made a complete recovery. At that time she said that her heart was not affected. Following this she was perfectly well until she was thirty, then she had another attack of severe rheumatism quite similar to the first one. After she had recovered from the acute symptoms of her second attack her physician told her that she had valvular disease of the heart. However, she paid very little attention to this and for some time felt perfectly well. At that time she was working as a stock clerk in a large dry goods establishment, this involved considerable lifting, her hours were long and she was on her feet all day. She said that she felt well and able to work and had no shortness of breath or other symptoms referable to her heart until about two months before her admission to the hospital. At that time she was greatly annoyed and somewhat alarmed by what she called "palpitation of the heart." This consisted of a tumultuous action of the heart of which she was uncomfortably conscious. Soon after this she began to be short of breath, and on going to her home, which was on the fourth floor, she was obliged to stop at the top of each flight of stairs to recover her breath. Soon after this she sought admission to the hospital on account of an attack of "bronchitis," this consisted of a feeling of constriction in the chest, cough, and a frothy mucus expectoration. In passing I want to call your attention to this group of symptoms of which so many cardiac patients complain and which they designate as "attacks of bronchitis," which are, in reality, not inflammatory in origin, but are due to chronic passive congestion. This is a point of considerable practical importance since these "attacks" are not at all affected by therapeutic measures suitable to relieve an inflammatory condition of the bronchial tubes, but are promptly abolished by securing a better circulation in the lungs.

To return to our patient. At the time of her admission to the hospital two years ago she was moderately dyspneic, lips somewhat blue, all over her lungs were heard coarse moist râles, most numerous at the bases, the abdomen was distended and

moderately tympanitic, there was slight pitting edema of both shins. The pulse-rate was 108, of fair volume, and Corrigan in type, it showed complete irregularity in force and time. The heart was definitely enlarged to the left, there were heard a systolic murmur at the apex and to the left as far as the mid-axillary line, also a diastolic murmur with maximum intensity in the third left space near the sternum, and audible in the second space on both sides of the sternum and as far down as the ensiform cartilage. The rate was 140 and was completely irregular. The sounds were of fair but variable quality. Her electrocardiogram (Fig 130) shows what you already have surmised, a condition of auricular fibrillation. The urine had a

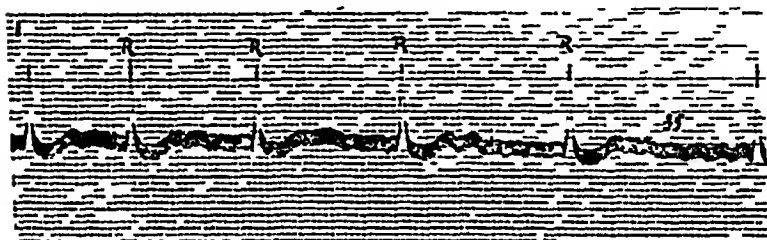


Fig 130—Case II Auricular fibrillation. Under satisfactory digitalization. Rate 68. Note complete irregularity, absence of P wave, *f* = auricular fibrillatory waves. Time intervals = 0.04 second.

specific gravity of 1022 and contained a heavy trace of albumin and a few hyaline casts. The diagnosis was chronic cardiac valvular disease of rheumatic origin, aortic insufficiency, mitral insufficiency, auricular fibrillation, dilatation and hypertrophy of the heart, cardiac insufficiency, passive congestion of the lungs and kidneys. At that time she was appropriately assigned to Class III, *1 c*, "organic heart disease with symptoms of cardiac insufficiency." She was put to bed, given a light simple diet, with fluids restricted to an intake of 1500 cc daily, and effective doses of digitalis were administered. She began to improve at once, at the end of ten days a count showed a radial of 68 and a heart rate of 68, the pulse deficit had entirely disappeared. The lungs were clear, the abdomen flat and soft,

there was no edema of the legs, the urine was normal Except for the slowing, the physical signs of the heart showed practically no change She was gradually allowed to increase her activities, and in six weeks appeared as she is today

As you examine her now you find the anatomic condition of her heart about as I have described it, the size, murmurs, and complete irregularity are still present The rate is 73, and there is no pulse deficit There are, however, no evidences of cardiac insufficiency, and when we question her we find that she is able to do her work as a seamstress, walk, climb stairs, and carry on her activities without symptoms of discomfort Her heart is doing the work necessary for her present mode of life, and today we may place her in Class II She must always avoid excessive physical exertion, her change of occupation has been an important factor in her present condition of health Emotional stress should be shunned, as this will tend to accelerate the heart and add an additional tax which she can ill afford She must avoid exposure to wet and cold and keep her general health as perfect as possible, so that she may be able to resist another attack of rheumatism and other forms of infection Since leaving the hospital she has taken each day a dose of the tincture of digitalis She must continue this for the rest of her life, at present she is taking 20 minims a day, she should be seen by a physician once in six weeks and the amount of the drug adjusted to her needs, the best guide being the heart rate, which should be kept about 70 Her present weight is 134 pounds, this is normal for her height, and her diet should be so regulated that she may keep as near this figure as possible

Case III—Chronic Myocarditis Cardiac Insufficiency at the Present Time—The next patient who will be presented is from the hospital wards He is a man seventy-two years old, a widower, and has been a canvasser, work which required him to be on his feet much of the time and to climb a great many stairs As a young man he acquired a gonorrheal infection which was followed by stricture, and later contracted syphilis In his younger days he was a heavy beer drinker, taking as many as thirty or forty beers daily, also whisky occasionally He has

drunk very little alcohol for the past five years. He does not use tobacco. Ten years ago he had a glycosuria which was treated for one year and then entirely cleared up.

Except for the above he has felt in excellent health until about four months ago, when he began to get short of breath on exertion. This gradually increased, and for the past five weeks he has been orthopneic. He stopped work on account of the dyspnea six weeks ago. He sleeps very poorly. Three weeks ago his legs began to swell. He has gained 12 pounds in the past three weeks. He has had no palpitation, no precordial pain, no headaches, no dizziness, no gastro-intestinal symptoms. He has to get up at night to pass his urine. He thinks the amount of urine has been rather scanty of late.

On examination we find an old gentleman whose tissues are all very flabby, propped up on pillows, he looks chronically ill, somewhat dyspneic, and moderately cyanotic. Over the right lung posteriorly there is evidence of a small amount of fluid in the pleural cavity. There are a few scattered, coarse râles over the remainder of the lungs. I have marked out an outline of the heart as it is made out on percussion. You will notice that it is somewhat enlarged to the left, the apex impulse is not palpable, heart sounds at the apex are very feeble, and here there is heard a soft blowing systolic murmur. At the apex is heard a galloping rhythm which is produced by a reduplication of the second sound. The heart is regular, rate 80. Blood-pressure systolic, 136 mm Hg, diastolic, 70 mm Hg. Abdomen soft, no tenderness, no abnormal masses, no signs of fluid. Liver and spleen not felt. There is marked edema of the legs. The urine is of low specific gravity, contains a trace of albumin, a few casts, no sugar. Chlorid output is normal. Blood urea 0.43 gram per liter. Phthalein output 31 per cent in a period of two hours.

The electrocardiogram which I will show you (Figs 131-133) presents a number of points of interest. The rhythm is regular. The P-R interval, that is, the time from the beginning of the auricular activity to the beginning of the ventricular activity, measures 0.23 second. The duration in this period

should not exceed 0.2 second, therefore in this case we have a delay in the time of conduction from the auricle to the ventricle, indicating a pathologic change in the bundle of His

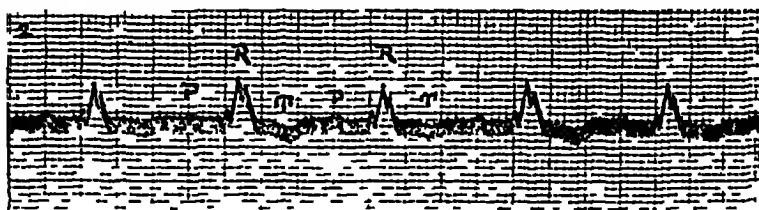


Fig 131

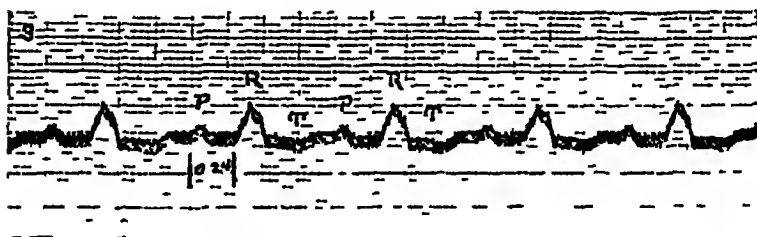


Fig 132



Fig 133

Figs 131-133—Case III Delayed conduction Arborization block
Note P R interval = 0.24 second R wave is of moderate height and limbs of wave are widely separated and notched

You will also notice that the complexes representing ventricular activity marked R and T are quite abnormal in outline (compare Figs 130 and 132) The R wave is of very moderate height and there is an abnormally wide period between its

beginning and termination, which measures 0.16 second, instead of being sharp sudden deflection, it is slow, notched, and of only moderate height. Such a deviation from the normal is indicative of a myocardial change in the ventricular wall and conforms to the condition described as "arborization block" in which the lesion involves the finer twigs of the conduction system.

This patient shows an advanced condition of cardiac insufficiency due to a degeneration of the muscle of the heart. Alcoholism and syphilis are quite adequate etiologic factors to account for this condition. This man should be assigned to Class III. He must be kept in bed for a considerable period. He should receive antiluetic treatment, means should be taken to increase the output of the kidneys. The outlook is a serious one. I should expect that with efficient treatment he would recover a reasonable amount of heart reserve and be able to do a little light work. However, it will be impossible for him to follow any occupation which will require much walking or climbing stairs. Unlike the second case which we have just examined, I do not expect that we will ever be able to transfer this patient to Class II. History, symptoms, and physical signs all point to a degree of myocardial change which will probably never support any considerable physical exertion or mental stress.

Case IV—Anemia Undernutrition Old Pleurisy Heart Murmurs Tachycardia Arrhythmia—This little girl is eleven years old, she attends the public school and is well advanced in her studies for her years, her mother tells us that she considered her a healthy, strong child until the past three months. She had measles when four years of age and a "pleuropneumonia" when she was nine, from both of which she made an uneventful recovery. No other illnesses, no sore throat, no snuffles, no growing pains. Her mother thinks that "she may pant a little more than other children" when she runs up the three flights of stairs to her home, but "the child never seems to notice it herself." The history reveals no other symptoms.

When we come to examine her we find that she is thin and

weighs 12 pounds less than the average child of her age, the skin and mucous membranes are pale, but not cyanotic. Temperature 98.4° F. Respiration 18. Pulse 110. Tonsils large and ragged, but showing no exudate. A few slightly enlarged lymph-nodes can be felt on the left side of the neck behind the angle of the jaw. In the left axilla can be heard a few leathery friction-rubs, otherwise the lungs are normal. The heart is normal in size and normally placed. The apex is palpable in the fifth space well within the midclavicular line. There are no thrills. The sounds are clear and of good quality, the pulmonic second is louder than the aortic second, there is no accentuation. The heart is rapid, always between 100 and 110,

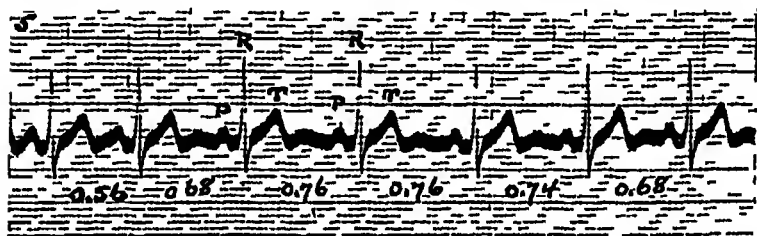


Fig 134—Case IV Sinus arrhythmia P = wave of auricular activity R and T = waves of ventricular activity Figures indicate length of cycles in fractions of a second

and shows a marked arrhythmia which is made more pronounced by forced respiratory movements (Fig 134). In the second left space near the sternum is heard a rather loud systolic murmur which is made more intense when the breath is held in the expiratory phase of respiration. At the apex is heard an inconstant systolic murmur, which is heard only during inspiration, and disappears when the breath is held. The blood shows a picture of a secondary anemia with 4,300,000 red cells and 70 per cent of hemoglobin. Leukocytes normal. Wassermann negative. Urine normal. The remainder of the examination shows nothing abnormal.

This little patient should be assigned to Class IV. She should be kept under observation for a long time and the con-

dition of her lungs and heart should be carefully followed. It is very improbable that she has any organic disease of the heart. The arrhythmia has its origin in the sinus node and is due to reflex nervous influences. Her electrocardiogram is shown in Fig 134. This arrhythmia is extremely common in children and young people, and is only significant of a rather active nervous mechanism. It should be recognized and distinguished from the more serious forms of irregularity. The modifications produced by forced respiratory movements help us in differentiating it from some of the other arrhythmias. The systolic murmur at the pulmonic area is very frequently heard in young people with flexible chests, it is rarely of pathologic significance. The inconstant systolic murmur at the apex is probably extracardial and due to her old pleurisy, you will note that it is only heard during the respiratory movements of the chest.

I feel very positive that this child has no organic disease of the heart. Her tonsils should have attention, her lungs should be watched for further evidence of active disease, her anemia and constipation should be corrected. Most of all, she needs to be built up with properly selected food. If this plan is followed, her tachycardia and arrhythmia will gradually disappear and in time even the murmurs may become inaudible.

This child is a representative of a very large class, in many of whom the evaluation of the symptoms is most difficult. I should like to spend the entire time of our conference this afternoon in discussing these and similar unusual physical signs and the significance of each one of them. The most important single element entering into your preparation to formulate correct interpretations in these cases is that you should personally examine a very large number of presumably normal individuals. By a large number I do not mean one hundred, but many hundreds, this is the only method by which you may familiarize yourselves with the limits of variability in the physical signs of the normal heart. The rigid examinations of the recent army drafts revealed not only a very large incidence of unsuspected organic heart disease but also taught the examiners many points in which the physical signs of the normal heart may deviate from

what they had hitherto considered the essential standards of an efficient organ

A well-balanced judgment based on a wide experience is essential to the welfare of these patients. If the signs are indicative of an organic heart lesion and if the symptoms suggest cardiac insufficiency, it is important that the damaged organ should be suitably protected. If, however, the physical signs have no pathologic significance and the symptoms arise from causes outside of the heart, it is of equal importance that the patient should not be stigmatized with the label "heart disease." You will see many individuals in whom such a designation has resulted in needless years of limitation and introspection. These habits once firmly established are exceedingly difficult to eradicate.

Case V—Acute Rheumatic Fever No Evident Heart Lesion—The last case which I wish to present to you today is a girl sixteen years old, who has been in the ward for the past three weeks, she is now recovering from her second attack of acute rheumatic fever. Her first attack was four years ago and she recovered from this without any apparent damage to her heart. The recent attack came on after exposure to wet and cold. For two weeks she had fever ranging from 101.5° to 102.5° F, with a heart rate of 100 to 120. Both ankles, both knees, and one wrist have been acutely inflamed, swollen, red, and tender. For the past week her temperature has been normal, the heart rate still is rapid (90 to 104). The signs of inflammation in the joints have nearly disappeared. The urine at one time showed a heavy trace of albumin, this has cleared up. At no time during her present illness has her heart shown any abnormal signs except the tachycardia, which might well be accounted for by the fever. The sounds are of good quality, the rhythm is normal, there are no thrills, no murmurs, and no other abnormal signs. We have no evidence that her heart has been injured and we must regulate our treatment and advice accordingly. This is the type of patient which may be regarded as a "potential" cardiac and therefore we should assign her to Class V.

Although we do not know the organism which has caused the arthritis and the constitutional disturbances, we believe it is an acute infection, and now that the constitutional symptoms have abated we may subject her to a searching study for the discovery and removal of any foci of infection or abnormal tissues which may have served as a portal of entry. If we find any such areas we will correct them as far as possible. She should be in the hospital at least two weeks longer, the length of stay depending on new developments or on the rate of her heart. I should prefer not to discharge her until the pulse is below 85, however, the tachycardia in these cases sometimes persists for months, and it is not possible to keep these patients in the wards for that length of time. The tachycardia alone will not be a contraindication to getting her out of bed. As soon as all signs of acute inflammation are definitely gone, and we have thoroughly corrected any defects of the tonsils, sinuses, etc., which we may find, we will permit her to gradually increase her activities by definitely measured amounts. At first the tendency will be to increase the heart rate, but if this persists for any considerable period after exertion, the exercise will be curtailed. Gradually the heart will respond to increased exercise with less acceleration, and the acceleration will be of shorter duration. This is a simple and reasonably safe guide, in this type of case, to the rate at which it is safe to increase exertion. This girl should go to a convalescent home for a stay of a month, where she will receive proper food and supervision. We may hope to see her return home sound and with a normal heart and circulation. It is quite certain that such a régime will prevent many a "potential cardiac" from ever becoming a subject of heart disease.

Someone will ask, Why include this last group under a classification of "heart disease"? The purpose is to direct attention to the possibilities of *prevention*. If you will remember what the life of a heart cripple means in limitation of education, curtailed capacity for work and play, years of suffering and economic loss to the individual and the community any measure which offers a prospect of avoiding damage to the heart will

assume a new importance You will pay more attention to "growing pains," chorea, recurrent tonsillitis, infections of the sinuses, carious and infected teeth You will guard more closely the convalescence from rheumatic fever You will urge the early and complete eradication of syphilitic infections You will have a new argument to present against the immoderate use of alcohol and tobacco

This grouping has already been found to be of practical value in transferring patients from one institution to another For example, the Burke Foundation and the Mineola Home for Cardiac Children, which received only certain types of patients with defective hearts for convalescence, require, as a condition of admission, that the class to which the individual belongs be designated on the application blank, and none are considered unless this condition is complied with

If you will put this classification into daily use you will find it of considerable service in focusing your attention on the functional capacity of the heart In directing the future activities of a patient with an established heart lesion, the most important question is *not* Has he mitral stenosis or aortic insufficiency? Has he a sinus arrhythmia? A premature contraction or auricular fibrillation?—but *What is the capacity of the heart for work?*

CLINIC OF DR ALBERT R LAMB

PRESBYTERIAN HOSPITAL

MULTIPLE SEROSITIS

WE have 2 cases today, gentlemen, which represent the early and late stages of a comparatively rare disease. They are not being presented because of their rarity alone although it is well for you to see the exceptional cases when opportunity offers, but because they are generally confused with some much commoner affections and are consequently, not diagnosed. And yet I believe that these cases offer us a sufficiently clear-cut clinical picture to allow all of you to approach them with a considerable degree of diagnostic confidence, once their salient features have been brought to your attention.

I shall present the more advanced case first, as it is most typical and shall proceed to one of a much earlier type, in which the diagnosis is much more difficult.

CASE I

The patient, a German, age sixty-five, was first seen by the late Dr Theodore C Janeway, October 28, 1898, and was correctly diagnosed by him after a short period of observation. The history as given at that time was as follows:

Family History—Mother died of a stroke. Father died of "Magenkrebs." No tuberculosis in the family. Wife has one child of two years well. She had four miscarriages in five years.

Past History—Had influenza in Germany in 1890 and a Neisser infection at the age of thirty-three. Otherwise always well.

Present History—In March 1898 caught cold and had "bronchitis" for seven months, but was confined to bed for only three

days His chief symptoms have been weakness, dyspnea on exertion, slight dry cough, with pain in the back He has also complained of poor appetite, epigastric oppression and pain after meals, with occasional retching and vomiting, constipation, inability to sleep, and the loss of 25 pounds in weight The dyspnea and pain in the back have prevented work and he is scarcely able to walk up one flight of steps No headaches and no hemorrhoids

Physical Examination —Skin dry and rough Acne on back Breathing slightly labored Left chest shows almost no expansion Slight venous pulse in neck Radial pulses equal, but rather weak Pupils normal Teeth, tongue, and pharynx normal Reflexes present and equal Heart sounds feeble and precordial dulness considerably increased, especially to the right

Lungs —Right shows definite signs of fluid from angle of scapula to the base Left shows dulness and friction-rubs over the precordium and at base of the axilla, while posteriorly below the angle of the scapula there are high-pitched voice, feeble breath sounds, and dulness The smooth firm edge of the liver is felt at the level of the umbilicus The spleen is not palpable

On October 31st his examination was practically the same, but there were signs of fluid in the abdomen He was not running a temperature Urine 1023, acid, trace of albumin, no sugar, trace of bile and many hyaline casts Leukocytes 8000, hemoglobin 80 per cent From that time until he came under observation at the Presbyterian Hospital in 1914, a period of sixteen years, he was seen from time to time by Dr Janeway In November and December, 1898 his right chest was aspirated three times, with the removal of 3200 c c of fluid His left chest was twice explored, but no fluid was obtained In July, 1899 7200 c c of fluid were withdrawn from his abdomen During the rest of this period none of his serous cavities required aspiration, although at odd times there were evidences of small amounts of fluid in his right chest and abdomen His liver was always palpable, but varied somewhat in size His spleen was never felt As a rule, he continued his occupation as cook Much of the time he felt very well, but at various periods com-

plained of some one or more of the following symptoms constipation, vertigo, lumbago, flatulence weakness dyspnea, palpitation and headache Cyanosis was observed on some occasions

When seen in March 1914 he was complaining of dragging abdominal pain His heart seemed to be of normal size and there were no murmurs Rate 84 B P 120 Lungs clear No fluid in abdomen Liver reached to the umbilicus, edge firm Spleen not felt Wassermann reaction negative Since that time he has been under constant observation, having been admitted to the hospital on fourteen separate occasions and followed in the out-patient department between admissions While at odd times there have been indications of fluid in his chest it has never been necessary to resort to aspiration

The story of his abdominal fluid is different, however, and is, perhaps, best shown in the following table

Date	Approximate interval.	Amount of ascitic fluid in cubic centimeters
July, 1899	First tapping	7,200
Oct 4, 1916	7 years, 2 months	1,500
May 25, 1918	1 year, 7 months	4,300
July 20, 1918	8 weeks	5,000
Dec 9, 1918	20 weeks	6,500
Jan 6, 1919	4 weeks	7,550
Jan 27, 1919	3 weeks	4,700
Feb 18 1919	3 weeks	6,900
May 12, 1919	12 weeks	7,650
June 19, 1919	5½ weeks	9,250
Aug 12, 1919	8 weeks	9,500
Aug 29, 1919	2½ weeks	8,000
Sept 22, 1919	3½ weeks	9,500
Oct 18, 1919	3½ weeks	9,650
Oct 24, 1919	1 week Operation	5,000 (approximate)
Nov 21, 1919	4 weeks	6,000
Jan 3, 1920	6 weeks	7,000
Feb 21, 1920	7 weeks	6,000
April 3, 1920	6 weeks	6,000
May 25, 1920	7½ weeks	6,000 (approximate)
July 21, 1920	8 weeks	7,500
Dec 4, 1920	19½ weeks	6,000
Jan 22 1921	7 weeks	7,000
Total		153,700

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palpable, well below the costal margin, and at the present time reaches nearly to the umbilicus. It is hard and the surface is irregular. There are no markedly dilated veins on the abdomen and no hemorrhoids. His blood count has been essentially normal throughout. Blood-cultures have been sterile. Blood urea 0.20 gm per liter. Phthalein 52 per cent.

The abdominal fluid has shown the characteristics of an exudate. On one occasion inoculation of this fluid into a guinea-pig gave a negative result. Cultures were always sterile.

Such, gentlemen, has been the story of this rather remarkable patient. Some of you are undoubtedly inquisitive as to the nature of the operation indicated in the table. This operation was performed by Dr. Eliot on October 24, 1919, and consisted in an intraperitoneal epiploxy. At this time we had the privilege of seeing Dr. Janeway's original diagnosis confirmed. The liver was readily seen extending well below the costal margin, it was cirrhotic in appearance, and the surface was as beautifully "iced" as any cake you have ever seen. The icing was fully 1 cm in thickness. The rest of the abdomen was not explored. Thus, it will be seen that in this patient we have to do with a perfectly characteristic case of so-called "Zuckergussleber." Most of you have probably heard of this condition, but I doubt if many have had the opportunity of seeing such a case, for, as I have already mentioned, the condition is comparatively rare.

Numerous other terms have been used for this group of cases: Pick's disease, pericarditic pseudocirrhosis of the liver, polyserositis, Concato's disease, chronic hyperplastic perihepatitis, polyorrhomenitis, and perivisceritis. Confronted by such a formidable array of names, we may, perhaps, more correctly appreciate the significance of this complex if we recall for a moment the historic background. In 1884 Curschmann described hyperplastic perihepatitis or "Zuckergussleber," a disease characterized by a slow, insidious and intermittent course, and persistent ascites, with a pathology similar to that in the case you have just seen, with the exception of the cirrhosis. He was not the discoverer of the condition, as it had been previously

It is astonishing to think of the sum total of fluid here given, the great bulk of which was removed in the comparatively short period of two and a half years

It would take too long to go into the detail of his bulky history, but the more important details may be summarized His course has varied, but, in general, I should say that he looks better and is more comfortable now than when I first saw him in 1914 He has certainly not gone down hill His disease has been afebrile His complaints have been weakness, dizziness, local precordial pain without radiation, constipation, abdominal discomfort, and, more recently, pain in the right shoulder Most of these symptoms have been more marked at the time when abdominal paracentesis was needed, and this operation was always followed by great relief His skin has always been dry and scaly, amounting to an ichthyosis Together with this you will note a peculiar gray cyanosis He has had an occasional attack of bronchitis with fever, but, in general, his lungs have shown nothing more than emphysema and râles of congestion at the bases, with, at times, indications of small amounts of fluid However, the x-rays have shown mottling and increased density of both lung shadows, with a dense patch 2 inches in diameter in the right lower lobe and irregular diaphragm shadows Several examinations of sputum have been negative for tubercle bacilli

In 1915 his von Pirquet reaction was positive, but in the following year it was negative, as was the tuberculosis complement-fixation reaction Since he has been under our observation he has been fibrillating, as shown clinically and by the electrocardiograph, and has been under digitalis rather constantly At one time his pulse suggested a paradoxicus, but this has never since been confirmed There have been no murmurs, but the heart sounds have always been distant and of poor quality There has been no Broadbent sign or fixation of the sternum There have been evidences of arteriosclerosis, as shown by the peripheral arteries and a double arcus senilis His blood-pressure has always been low 120/75, 95/60, 108/65, 100/60, etc His spleen has not been felt His liver has always been

changes in other tissues and organs—notably pleuritis, peritonitis, perihepatitis, nutmeg liver, red atrophy of the liver, cirrhosis of the liver, etc.” He admits that in thus “presenting the complex of obliterative pericarditis with ascites there are grouped a number of cases that differ more or less in nature the one from the other.”

In 1918 Evans attempts an even broader classification, and in admitting our ignorance of the underlying factors believes that “until further investigation presents more light on the etiologic factor or factors causative, multiple serositis should not be restricted to a clinical picture necessarily associated with adhesive pericarditis or perihepatitis, which, after all are probably but conditions incident to the general serous involvement rather than responsible for it.”

Until more is known I think that you will all agree in designating the multiple serositis as the essential feature of this group of cases, for not all of them have “iced” livers, nor do all have adhesive pericarditis.

In this group of cases the sexes are about equally divided. In Kelly's cases about 60 per cent began before the age of forty.

The cause of the disease is not known. That is the most important reason for grouping all these cases together until the etiology is settled and a proper segregation can be effected. The tubercle bacillus has been accused more frequently than any other organism and is most certainly accountable for some of the cases. The part played by this organism in causing adhesive pericarditis is well recognized. Hamman, in speaking of tuberculous peritonitis, considers it under three divisions:

(1) As a local tuberculous disease, just as one speaks of pulmonary tuberculosis as a local tuberculous disease.

(2) As one manifestation of the whole course of tuberculous infection.

(3) As part of a disease affecting the large serous cavities.

It is only with the third variety that we are concerned at present. He admits the close relationship of this group to the cases which we are considering, but inclines toward keeping them in a separate category. One fact stands out, and that is,

recognized by Rokitsansky, Bamberger, Murchison, Wilks and Moxon, and Fagge, but he did elaborate the picture, and his name has become linked with it as has none of the others. Curiously enough, however, I venture to say that most of you have associated the name of Pick with "Zuckergussleber," although his publication did not appear until twelve years after Curschmann's. He took a broader view of the complex than did the latter, including cases of "Zuckergussleber," but not limiting the group to that one form. Pick laid most stress upon the adhesive pericarditis as the primary event, leading to disturbances in circulation which caused connective-tissue hyperplasia in the liver and the consequent picture of recurring ascites, enlarged, firm and irregular liver, without edema of the legs. For this condition he proposed the name of "pericarditic pseudo-cirrhosis of the liver," a designation which should be synonymous with Pick's disease as applied by later authors. While his communication stimulated interest and added knowledge to the picture, he can no more be regarded as a pioneer in the field than could Curschmann, for van Deen reported a case as early as 1846, and some fifteen authors wrote on the subject before Pick.

In Italy this group of cases has been known as Concato's disease, polyorrhomenitis, or polyserositis, while in France the name perivisceritis has at times been used.

Enough has been said to indicate, as pointed out by Rolleston, that we have had portrayed to us two more or less different pictures. "The so-called Pick's disease, in which the predominating condition is the nutmeg or cardiac liver, characterized by venous engorgement, later by red atrophy, and ultimately cirrhosis, on the other hand, those cases of multiple serositis in which the perihepatitis is the prominent clinical feature. Both conditions present at autopsy 'pericardial lesions' " (Evans)

In his admirable monograph on "Multiple Serositis," published in 1903, Kelly renders a distinct service in grouping them all together as "cases characterized clinically by marked ascites, with little or no edema of the legs, cases in which the diagnosis of cirrhosis of the liver is usually made, and which at the necropsy reveal chronic obliterative pericarditis and certain morbid

changes in other tissues and organs—notably pleuritis, peritonitis, perihepatitis, nutmeg liver, red atrophy of the liver, cirrhosis of the liver, etc.” He admits that in thus “presenting the complex of obliterative pericarditis with ascites there are grouped a number of cases that differ more or less in nature the one from the other.”

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that the type of lesion is different from the ordinary tuberculous peritonitis. The only other etiologic factor which has been convincingly brought forward is rheumatic fever. And so we find ourselves in the position of believing that the disease represents a chronic inflammation of various serous membranes and that the etiologic factor may vary in different cases.

While there has been much discussion about the pathogenesis of the condition, it seems to me that Kelly's explanation still stands as the most plausible. He first points out that, as shown by the experimental work of Clark and others, "fluids and solids may pass through the endothelial layer of the diaphragm, the fluids in many places, the solid particles only through the central tendons of the diaphragm—minute particles are carried in an incredibly short time from the peritoneal cavity through the diaphragm into the mediastinal lymph vessels and glands and thence into the blood circulation—there is normally a force in the peritoneal cavity which carries the fluid and foreign particles toward the diaphragm." Arguing from this, he says, "the attempt on the part of the peritoneum to remove certain noxious agents may result in partial or complete success. In the latter instance the peritoneum may be completely rid of the infective agent, which, being carried to the mediastinal lymph glands may infect the pericardium or the pleura—subsequently the peritoneum may become infected. In other cases the attempt on the part of the peritoneum being only partially successful the region about the liver and the under surface of the diaphragm succumbs and a primary perihepatitis occurs—subsequently, the infective agent may travel through the diaphragm and infect the pericardium or the pleura, or both. In these cases, on account of the peculiar lymphatic supply of the liver and the under surface of the diaphragm, the infective agent being, as it were, concentrated to the region about the liver, especially to the neighborhood of the suspensory ligament toward which many of the lymphatics converge, gives rise to the excessive and often hyperplastic lesions sometimes observed. In a number of cases, on the other hand, a primary pericarditis occurs independently of peritoneal infection. Following such

initial infection of the pericardium the other serous membranes may become implicated, and in some cases all the serous membranes become infected at the same time by the same infective agent "

Anatomically the disease is characterized by chronic hyperplastic inflammation of the various serous membranes, and in many cases by the thick, white, almost cartilaginous fibrous tissue which coats the organs, especially the liver, giving the appearance of confectioner's icing

How are we to recognize these cases clinically? As I have mentioned to you before in connection with other diseases, the first essential is to remember that such cases do exist, so that when you see a patient whose striking symptom is recurring ascites you will consider multiple serositis and see if you can either establish the diagnosis or rule it out, remembering that the only two important diseases with which it is usually confused are cirrhosis of the liver and tuberculous peritonitis. As a rule these patients do not have the alcoholic history which you would expect in ordinary cirrhosis of the liver. Again, in many of them, as in the one you have just seen, there is a history of previous involvement of one or more serous membranes—a pericarditis, a pleuritis, or a perihepatitis. Following such an attack, it may be years before there is further noticeable progress in the disease. In some cases one can trace the involvement of one serous membrane after another. When present, such a sequence of events helps greatly in arriving at a diagnosis, but we must remember that frequently such aid is lacking and that we must fall back upon the all-important ascites—an ascites which is "characterized by the fact that it is excessive, that it necessitates repeated tapplings, that it recurs rapidly after tapping, and that it may remain stationary (not necessitating tapping) for many years "

The onset of the disease varies somewhat according to the region first affected. Thus, one may have early peritoneal involvement with attacks of perihepatitis—pain, tenderness, rigidity, and possibly palpable and audible friction-rubs in the right upper quadrant—in which case ascites is an early mani-

festation, with leg edema absent or later. On the other hand, the picture may be ushered in by a pericarditis, in which case one is more apt to find early edema of the legs and late ascites. The course is remarkably slow and noted for its periods of remissions, but as it goes on we must bear in mind that while some of the symptoms are due to the serositis, many are the result of cardiac insufficiency.

The important findings are the signs of adherent pericardium, the ascites, signs of fresh or old pleuritis, the absence or early occurrence of leg edema with its subsequent disappearance until late in the disease, the markedly enlarged and rather uneven liver without the anticipated evidences of collateral circulation and portal congestion, the absence or late development of a corresponding enlargement of the spleen, and the absence or transient presence of jaundice. The fact that the patient survives a large number of abdominal aspirations—one case was tapped 301 times—is of very great weight in the diagnosis. In Kelly's collected cases the duration of the disease was over ten years in 3, and between two and five years in 35.

It is at once evident that our first patient today presents a remarkably characteristic picture of multiple serositis with the exception of his alcoholic history. It is interesting to note that following his epiploexy the tapplings have been rather less frequent and of smaller amounts.

Having shown you such a typical case, it will now be interesting to give you a résumé of another case, much less clear, in which no one even suggested the correct diagnosis. It is perhaps of even more value in another way, in that an intercurrent infection cut short the disease in which we are interested in its early stages and gave us the opportunity of studying the early lesions.

CASE II

M S. A married woman of fifty-eight entered the hospital October 19th, and died November 21st.

Family History—Her son and an uncle died of tuberculosis.

Contact with the former was intimate some ten years before her present illness. A sister died of breast cancer.

Personal History—Born in Switzerland, leaving there at the age of twenty, and after several years in France and England came to the United States, where she has since lived. Best and average weight 135 pounds three years ago. Has been losing for the past year, and now weighs about 100 pounds. Tea, 2 cups, coffee, 1 cup occasional glass of beer. Good appetite. Bowels regular. Sleeps well. Married twenty-eight years. Husband well. Only son died of tuberculosis at sixteen. No miscarriages. Menopause ten years ago.

Past History—Always quite healthy. Lived in good surroundings.

Present History—A rather vague story which was difficult to piece together. About three years before admission she began to lose weight and strength without any other symptoms. There were varicose veins of her legs and one year ago she had an operation for these.

Some two years ago she had some skin affection of the hands and later a papular rash on her arms, shoulders, and back of the neck. At this time her hair and eyebrows became scanty. About one year ago she had a rash on her face. This was red at first and has only recently turned brown. As time has gone on she has lost more weight and strength, especially in the past five months. Six weeks ago she began having stabbing pains in the epigastrium, sometimes sharp, at other times dull—no radiation to the back or shoulder. These pains had no reference to meals, but rather to fatigue. One month ago, while at another hospital, she had a secondary anemia, a negative Wassermann, and a chest x-ray which was reported as showing a mass the size of a baseball just above the diaphragm, pushing the heart to the left. No trace of such a shadow was found in our x-rays. For three months there has been dyspnea and occasional palpitation, but no cough.

Physical Examination—Temperature 101° F, pulse 104, respirations 28. Undernourished, pale, middle-aged woman, sitting up in bed, suffering from a peculiarly uneven dyspnea.

and presenting a rather startling appearance, owing to the moderate exophthalmos and wide palpebral fissures, together with the patchy brown pigmentation, surrounding areas of white skin Dr Fordyce considered that this pigmentation was simply part of some constitutional disease, such as tuberculosis or carcinoma of the gastro-intestinal tract Hair and eyebrows scanty Ears negative The pupils are small, slightly irregular, and somewhat sluggish in their reaction No nystagmus The eye-grounds show marked arteriosclerotic changes in the vessels Aside from slight pyorrhea, the teeth are in good condition Pharynx normal There is no thyroid enlargement, tracheal tug, or lymph-gland enlargement Heart area of dullness

10 cm	I	30 cm
15 "	II	40 "
	III	90 "
	IV	11 6 "
	V	12 5 "

Apex in fifth space 1 cm outside nipple line No thrills Sounds are of good quality and regular, but the action is quite rapid There is a soft blowing systolic murmur at the apex without transmission, heard also along left sternal border Aortic second sound is greatly accentuated Blood-pressure, 170/70

Lungs—Expansion fair and equal On right side posteriorly there is an area of dullness extending from beneath the angle of the scapula to the base, but not far into the axilla Over this area the breath and voice sounds and fremitus are diminished No râles are heard except for a few crackles at the left base Breath sounds over the rest of the chest are of somewhat emphysematous quality

Abdomen—There is considerable resistance, especially in the right upper quadrant, but no tenderness No masses felt Liver and spleen do not percuss enlarged, nor can they be felt There are pigmented scars over both legs resulting from the varicose vein operation No pathologic reflexes No edema

Laboratory Findings

Blood culture	Sterile.		
Blood Wassermann	Alcoholic +		
	Cholesterin +		
Blood urea	0.72 gram per liter		
Lumbar puncture	15 c. c. clear fluid under normal pressure		
	Cells, 4 lymphocytes		
	Globulin, 0		
	Colloidal gold curve, 1 2 3 3 2 0 0 0		
	Wassermann	2 c c	0.6 c c.
	Cholesterin,	Neg	Neg
	Alcoholic,	Neg	Neg

Phthalein 20 per cent

Course—Patient ran an irregular temperature between 100° and 103° F, with a rise to 104.5° F, with her terminal pneumonia. X-Rays showed an enlarged heart and some increased markings in the lungs, especially at the right base. The urine contained neither melanin nor homogentisic acid (alkapton).

On admission her *blood count* was R B C, 2,700,000 W B C, 3700 Hg, 47 per cent Polys, 85 per cent Lymphos, 13 per cent Trans, 2 per cent.

Urobilin in urine, none Urobilin in stool, 4400 dilutions

On November 1st Dr. Howe reported her neurologic examination negative, except for the pupillary changes, which he considered due to arteriosclerosis. Stool examination negative.

November 5th R B C, 1,968,000 Hg, 45 per cent W B C, 1920 Polys 72 per cent Lymphos, 24 per cent Trans, 4 per cent. Smear shows very slight anisocytosis and poikilocytosis. No nucleated red cells. Platelets markedly diminished.

November 12th Blood Wassermann, alcoholic negative, cholesterian negative.

Gastric Analysis

	HCL	Total acid	Blood	Bile	Amount and appearance
Fasting expression	0	+		0	Few drops
One half hour	0	1S	+ Fresh	0	5 c c.
One hour	0	1S	+ Fresh	0	5 c c.
One and a half hours	0	—		0	Less than 1 c c.
Two hours	0	+		0	Less than 1 c c.
No lactic acid					

On November 10th she developed a peculiar transitory edema of the right eyelids and conjunctiva

November 16th Blood-pressure 155/60 right arm, 148/58 left arm Blood urea 0.47 gram per liter Stool examination negative

November 17th Owing to her extreme anemia she was given a transfusion of 500 c.c. citrated blood

This was followed by a marked improvement in her condition and blood count Two days later she developed a Group I pneumonia with positive blood-culture, which caused her death on November 21st

Urine examination—specific gravity 1015–1020 Albumin faint trace, few hyaline casts

Autopsy by Dr. Von Glahn—The subcutaneous fat is of a golden yellow color, moderately firm, and about 2 cm. in thickness The omentum is adherent to the anterior abdominal wall by firm, fibrous adhesions and contains a moderate amount of fat and also considerable black pigment scattered through it The peritoneal cavity does not contain an excess of fluid The colon is moderately distended and the head of the cecum is bound to the parietal peritoneum by dense fibrous adhesions The appendix is free There are some recent delicate fibrous adhesions between the uterus and the mesentery of the sigmoid The liver extends 5 cm. below the xiphoid There are numerous, delicate, fibrous adhesions between the liver and the under surface of the diaphragm

Thoracic cavity There are numerous fibrous adhesions between the right lung and the parietal pleura The same condition obtains on the left side, where, in addition, there is a considerable quantity of fluid The pericardium is adherent to the heart

The heart and pericardium weigh 600 gm The pericardial sac externally on the side next to the left lung is covered with a fibrinopurulent exudate and the vessels in it are very much injected In the posterior part of the pericardial sac there is a slight accumulation of fluid and here the surfaces are covered with a fibrinopurulent exudate Elsewhere the pericardial sac is adherent to the heart by edematous fibrous adhesions The foramen ovale is widely patent The various valves are normal

except for a moderate amount of sclerosis of the mitral and aortic. The coronaries show very early sclerosis without calcification. There is some tigering of the papillary muscles of the left ventricle. The myocardium is rather brown in color. There is no evident increase in connective tissue. The aorta shows numerous yellow, elevated plaques, particularly around the openings of the intercostal arteries, and these plaques become more numerous as one approaches the bifurcation. There is slight calcification of one of the plaques at the bifurcation. None of the suggestive marks of syphilis. Left lung. The pleura is everywhere covered with a fibrinopurulent exudate. The lung is adherent to the pericardium, the parietal pleura and the two lobes are glued together. The lower lobe is consolidated. Right lung. There is no evident consolidation. The lower lobe is atelectatic. The pleura shows recent and old pleurisy. Spleen weighs 80 grams. The capsule is slightly thickened in one or two small places. The pulp is dark red in color. In the lower pole there is a firm opaque yellowish area which stands out in marked contrast to the surrounding pulp and which measures 4 mm in its greatest diameter. There is another similar but smaller area in the lower margin. Pancreas normal. Liver weighs 1720 grams. The capsule over the left lobe is smooth, while that over the right lobe is roughened by fibrous adhesions, binding this lobe to the diaphragm. Through the capsule the liver has a mottled red and yellowish appearance. The lobulation is uniform throughout. The central part of the lobule is reddish gray, while the part around the portal vein is reddish yellow. The liver seems quite firm in consistence, but there is no apparent increase in connective tissue. In the depths of the right lobe there is a tiny gray, translucent nodule apparently located in the portal area. Gall-bladder normal. Adrenals quite normal. Kidneys resemble each other in all respects, each weighing 150 grams. Surface very finely granular. On section the cortex is narrowed in places. The striations are straight for the most part, but in places are indistinct. Bladder normal. Uterus shows senile changes. Ovaries. There are numerous adhesions between the right ovary

and the parietal peritoneum. The end of the tube is closed by an adhesion. This ovary contains a small cyst. The tube is slightly distended with fluid. The left ovary is surrounded by a few adhesions, but is otherwise normal. Stomach and intestines present no abnormalities. The bone-marrow from the femur is in places grayish red, while in other parts it is yellow and very fatty. Larynx negative. The lobes of the thyroid are slightly enlarged. In the left there is a sharply circumscribed area surrounded by a yellow margin, the central portion of which is somewhat homogeneous, with a dark, reddish-gray nodule near the periphery. The mass is $\frac{1}{2}$ cm. in its greatest diameter. In the right lobe there are several smaller nodules, one of which has a small hemorrhage in its center. The brain and nasal sinuses are essentially normal. There is a caseous lymph-gland lying along the aorta over the lumbar vertebrae.

The microscopic examinations in this case are not yet completed, but sections of the nodule in the spleen and of the caseous lymph-node show a characteristic tuberculous lesion.

This patient apparently represents the type of multiple serositis due to tuberculosis. I do not see how the diagnosis could have been made or even suspected in the absence of ascites. The picture was remarkably complex, with the peculiar pigmented skin lesion, the evidences of hyperthyroidism and general arteriosclerosis, and the extreme anemia. She also showed more or less fever throughout the period of observation which is not a characteristic of multiple serositis. As the autopsy showed an old adherent pericardium and bilateral pleurisy, with old and recent perihepatitis, peripleuritis, and peritonitis, I do not see how we can escape the conviction that she suffered from the disease which we have discussed today.

I trust that these patients will make cases of ascites more interesting to you, and that, bearing in mind the important points which we have outlined, you will have the opportunity of recognizing multiple serositis in the future.

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CONTRIBUTION BY DR GEORGE DRAPER

FROM THE ENDOCRINE CLINIC, PRESBYTERIAN HOSPITAL

REVERSIVE SECONDARY SEX PHENOMENA

Introduction—Every branch of medical literature today is filled with discussions of the glands of internal secretion. The subject has engaged the attention of workers in every field of medicine, and consequently many angles of approach to its elucidation have been seized upon. Many valuable facts have been uncovered, some through research laboratories of biology, some through the clinic. It is perhaps easier to get facts in the former place than the latter because not only are the experimental conditions more readily and rigidly controlled, but because the observer in the laboratory is not subject to those subtle and often deluding influences which are distilled from the contact of the personalities of patient and physician. Still it is quite as possible today to make accurate observations of fact in the clinic as it ever was. But there is a temporary danger that inaccurate observations will be made and unsound deductions drawn as a result of the new opportunity for pure clinical study which the increasing knowledge of the endocrine glands has given to every physician. The great advances in laboratory method for a time seemed to throw the practitioner, the physician who met sick men face to face, a little on the defensive. The habits of the laboratory—accuracy and control—had not been instilled through his medical education to the degree demanded by workers in the so-called pure—which perhaps really means impersonal—sciences. And so the technic of the doctor became unduly though illogically limited through the restraining influence of accurate laboratory methods. Now the rays of knowledge of the endocrine glands have again projected

the human being upon the screen as an object for direct observation by the physician. The danger of the situation is obvious. Hypothesis will again run far ahead of fact and be used as though it were fact.

The following cases are presented, so far as possible, simply as objects for study. No attempt will be made to elaborate hypothetical explanations. But attention will be drawn to comparison with whatever facts are known. In a sense the cases speak for themselves, and they are offered as typical examples of those endocrinopathic states which are perhaps most definitely established, and which, therefore, may best serve as standards against which to measure less intensely pathologic forms, and later the more subtle differences of constitution which may depend upon slight glandular disbalance.

CASE I

H A Chief complaint lack of masculinity dating from boyhood. Father and mother medium-sized people. Five brothers and 2 sisters, all healthy, 1 brother has 10 children. Up to age of seven or eight he was not so fat, after that he gained rapidly. Doesn't know about his dentition history. Began to notice small genitalia at age of ten years. Erections began about this time. Never had emissions, never intercourse, never masturbation. Psychic eroticism apparently neutrally directed, possibly a trifle toward the male. He objects to hearing men talk of their exploits with women.

Patient is never constipated. Appetite uneven, sleeps well, but dreams much. Patient is very unhappy about his condition. Has always been able to work—ship boy and cook—but has been forced to leave every job because of the tormenting jibes of his mates.

Had measles severely ten years ago, no typhoid, scarlet, or mumps. Tonsillitis three or four times.

Has had four operations. Incontinence, retention, undescended testis, perforation of abdomen from pulling on a nail, followed by peritonitis, appendicitis.

Two years ago was knocked unconscious—probably fracture

of skull, has had headaches since no dizziness, made worse by worry or excitement

No eye symptoms Both ears discharged for many years
No deafness

Bowels always regular

Patient weeps easily, reaches for the examiner's hand and all gestures and expressions are feministic

Eczema of neck and ear, herpes of lower lip

Tongue large smooth, red, no tremor

Teeth, few remaining in bad condition

Lungs clear heart negative

Abdomen many scars of operation

Massive fat

Genitalia Penis 3 cm long, 1.5 to 2 cm in diameter

Reflexes sluggish

Voice, soprano

Blood count Hemoglobin 76 per cent R B C, 4,800,000
W B C 8800 Polynuclears, 55 per cent Small lymphocytes, 29 per cent. Large lymphocytes 7 per cent Large mononuclears, 1 per cent Transitionals 4 per cent Eosinophils 4 per cent

Urine, negative

Sugar tolerance.

Blood Fasting, 1.0 gm
Two hours, 0.95 gm

Blood W R., alc neg
chol, --

Urine

Four hours after, no sugar
Six hours after, \ F T

Basal metabolism, + 8 per cent

Thermal reaction to anterior lobe pituitary extract

Temperature, 1 hour post injection, 99.2° F
2 hours post injection, 99.6° F
3 hours post injection, 99.6° F
4 hours post injection, 100.2° F
5 hours post injection, 99.4° F
6 hours post injection, 99.2° F
7 hours post injection, 99.4° F
8 hours post injection, 99.0° F
9 hours post injection, 99.0° F

Discussion.—This case, then, presents the following characteristics Enormous adiposity associated with slightly above average height, but the length of the extremities is greater than that of the trunk Thus in the general conformation of the

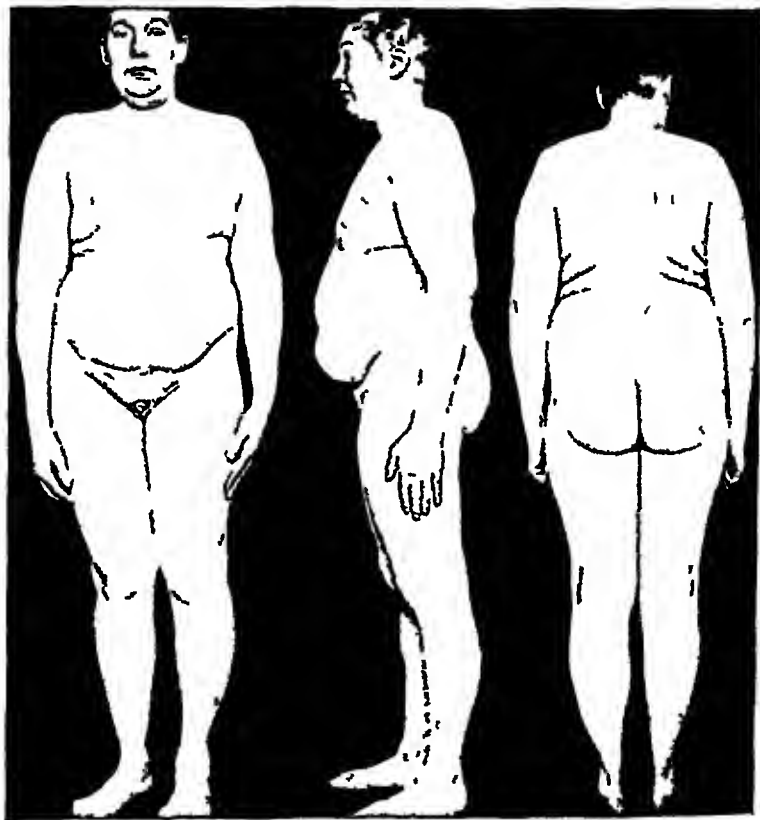


Fig 135—Case I Observe breadth of hips and feminine expression of face, genu valgum, and development of the leg at the outer side Observe also the scars above and to the outer side of nipples, possibly the site of transplantings Diagnosis Eunuchoidism

body are found the characteristics described by Tandler and Gross as typical of the castrate These authors describe two forms in which the castrate appears in about equal frequency (1) greater than average height, rather spare, and with the

Furthermore, they point out that in the male castrate the skeletal changes are not essentially toward the female type of skeleton, but toward what may be termed a less definitely masculine skeleton. In female castrates there is a similar modification of the skeleton away from the characteristically feminine form. In other words, the skeletons of castrates of both sexes converge toward what may be called a neutral form, sometimes considered to be the pure species form of skeleton, uninfluenced by secondary sex attributes. The outstanding features of these changes are the greater length of the extremities and trunk, and the greater width of the pelvis in relation to the shoulders.

It will be observed that this patient presents an extraordinarily wide pelvis and that the disposition of fat is feminine. Furthermore, there is a definite genu valgum, and the bulge of the calf of the leg is distinctly to the outer side. Consequently, there seems to be a suggestion that in this individual there is something more than the simple reversion to a pure species type of skeleton, indeed, that there may be definite feminine traits.

In this connection it is interesting to consider for a moment the psyche of the individual. He is extremely emotional, tends to apply for advice and help to any one who shows the slightest willingness to listen to his troubles, and reaches out for the hands of his hearers. These he takes impulsively, and with tears in his eyes beseeches assistance and sympathy. Furthermore, he cannot abide listening to the rough talk of his shipmates when they tell of their exploits in venery. He says he cannot hear women spoken about in such fashion. In every respect, therefore, the patient presents a strikingly feminine psyche. It has been difficult to determine to which sex the individual's eroticism belongs, but the impression has been gained that it is very moderate or almost absent, though, if anything, slightly directed from the female toward the male.

From these considerations we are justified in concluding that this individual at all events can be compared very accurately in most details with the second type of castrate, according to the descriptions of Tandler and Gross. Whether or not the greater indications of femininity which this individual presents justify

us in assuming the presence somewhere along the genital tract of ovarian rests is open to question, but it seems highly probable. The patient himself states that he was aware of genital inferiority at the age of ten. In the absence of any positive mumps history we are, therefore, forced to the conclusion that he is a true example of congenital gonad insufficiency—the classical eunuchoid.

Whether or not this individual could be metamorphosed by a successful transplantation of testicular tissue is open to question. If he does possess ovarian rests, testicular transplants would fail, according to the experiments of Steinach. It has been impossible to get any information about the symmetric wounds over the breasts, but one cannot help hazarding a guess that they represent an attempt at transplantation.

CASE II

T. C. Male, age forty Italian

Chief Complaint—Constipation

Family History—Father a large man. Mother very stout. Brother and sister both fat and healthy.

Personal History—Patient doesn't know whether he was a large or small baby. Was "skinny" at six to seven years. Average size as youth. Began to get fat sixteen years ago (at twenty-four). Never had any pubic hair till thirteen to fourteen, then very scant. Knows nothing about dentition, but never had trouble with his teeth.

Past Illness—Patient has always had tendency to constipation. At sixteen years of age had very bad attack of intestinal catarrh, with terrific constipation. Many nightly emissions. Since seventeen to eighteen years almost every night. For past five years constipation very bad and has tried all kinds of medicine. Now is taking 3 grains pituitary extract daily, and is better he thinks. Patient thinks he passes a good deal of water. He gets tired easily. He has had a sort of headache across the forehead for a long time, lately it has been rather more intense. Sex activity considerable from twenty to thirty. Lately some diminution both in libido and potentia.

• Appetite poor. Doesn't sweat much. No hives.

Patient had orchitis at eighteen—not gonorrhea This he had at age of thirty-three No measles Pneumonia at nineteen No scarlet and no diphtheria Sore throat once a year Metabolism determination, November 15, 1920, + 8 per cent

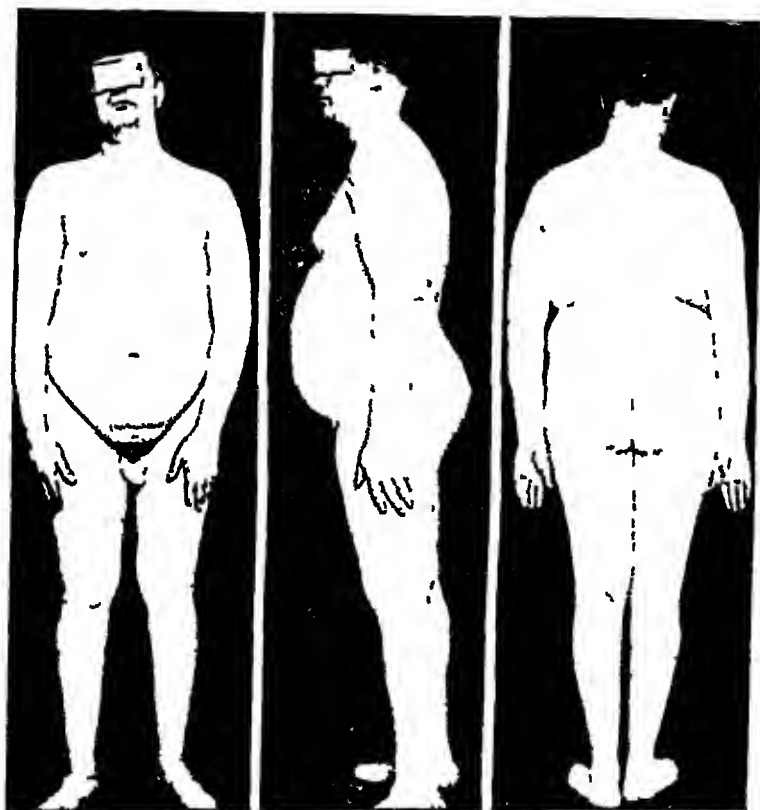


Fig 137—Case II Observe the less marked but similar outlines to Case I Marked mons veneris, and development of calf to the outer side Also the fatty tissue in the breast region Diagnosis Incomplete gonadal insufficiency

x-Ray report, 12/6/20 Sella is long, no flattening of the clinoids, no erosion No indication of increased intracranial pressure

Discussion —This patient is a distinctly successful individual

in many respects He is very clever and purposeful in his business dealings Notwithstanding the absence of virile physical secondary sex characteristics, masculine eroticism is

NAME T C	AGE 40	SEX Male	NATIONALITY Italian
HEAD Shape Low short - round			
FACE Short - oval		PROFILE Rather flat with slight over closure	
EYES Deep set, medium	INTERPILARY SPACE 7 mm.		
Oculomotor 0	MOTIONAL Slight Delirious		
Color Eyes grey	ALPHERAL PICTURE	Not medium short - 40 - medium narrow - not slightly to brow angled	
Oculum Slightly puffy upper lid	SQUINT 0		
GLABELLA Entire prominent	SUPRAORBITAL RIDGES Broad - flat		
NOSE Eye-Large-medium-front	FORM Pointed		
EARS Eye-Large-medium-front	SHAPE Everted oblong	LOBE Large	
JAWS Pseudo Arch High-set and close-together		DENTAL Arch-broad-medium-narrow-angled	
TEETH Spacing Close set		Medium oval	
Shape Broad, short		QUALITY Poor	
Position Eyes		COLOR Opaque	
HEIGHT 168 5 cm.	WEIGHT 211 lbs		
ARMS Thinly 271 cm			
TRUNK Length 87 5 cm.	LOWER EXTREMITY Length 91 5	RATIO	
HANDS Eye-Low-medium-front	FINGERS Flat 1 - 4 - 5 - 6 - 7 - 8 - 9 - 10 - 11 - 12 - 13 - 14 - 15 - 16 - 17 - 18 - 19 - 20 - 21 - 22 - 23 - 24 - 25 - 26 - 27 - 28 - 29 - 30 - 31 - 32 - 33 - 34 - 35 - 36 - 37 - 38 - 39 - 40 - 41 - 42 - 43 - 44 - 45 - 46 - 47 - 48 - 49 - 50 - 51 - 52 - 53 - 54 - 55 - 56 - 57 - 58 - 59 - 60 - 61 - 62 - 63 - 64 - 65 - 66 - 67 - 68 - 69 - 70 - 71 - 72 - 73 - 74 - 75 - 76 - 77 - 78 - 79 - 80 - 81 - 82 - 83 - 84 - 85 - 86 - 87 - 88 - 89 - 90 - 91 - 92 - 93 - 94 - 95 - 96 - 97 - 98 - 99 - 100 - 101 - 102 - 103 - 104 - 105 - 106 - 107 - 108 - 109 - 110 - 111 - 112 - 113 - 114 - 115 - 116 - 117 - 118 - 119 - 120 - 121 - 122 - 123 - 124 - 125 - 126 - 127 - 128 - 129 - 130 - 131 - 132 - 133 - 134 - 135 - 136 - 137 - 138 - 139 - 140 - 141 - 142 - 143 - 144 - 145 - 146 - 147 - 148 - 149 - 150 - 151 - 152 - 153 - 154 - 155 - 156 - 157 - 158 - 159 - 160 - 161 - 162 - 163 - 164 - 165 - 166 - 167 - 168 - 169 - 170 - 171 - 172 - 173 - 174 - 175 - 176 - 177 - 178 - 179 - 180 - 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Fig 138—Case II

highly developed and potentia is considerable, possibly a little greater than average He feels muscularly strong and has no complaints, save that of his obstinate constipation Certain features in this patient's anatomy are interesting from the point

of view of their comparability with similar points in the acromegalic. There is great prominence of glabella, with unusual breadth of nose bridge, and the interpupillary distance is wide, 7 cm. The thorax is deep and short, and its subcostal angle wide with a large ensiform. Furthermore, as in Case I, this patient's lower extremities are longer than his trunk, and his span exceeds his height, features which seem clearly associated with increased activity of the pituitary gland when there is gonadal inadequacy in early life. It is quite evident, however, that if the castrate length growth phenomenon is due to the removal of testicular influence, there must be one specific activity of the gland concerned in the process. For in both Case II and Case III, notwithstanding the presence of this phenomenon, the adiposity and scant hair, there exists an unusually active libido and potentia.

Another question which likewise will bear consideration is that of adiposity and feminine contour. All cases of the type under discussion develop the characteristic contour which is commonly associated in everyone's mind with feminism. But women develop an identical adiposity which is more than an exaggeration of the accepted female form—it is an actual difference. Is this adiposity found both in women and men, perhaps a neutral characteristic, and like the skeleton of the castrate, a form which tends away from sex toward species? In this connection it is helpful to remember that in the aged of opposite sex there is a convergence of habitus not only of the body, but of the mind—the exact reverse of the divergence seen in adolescence.

Therapeutically, Case II has offered a most difficult problem. On large doses of pituitary and thyroid extract he has felt much stronger and more active. But there has not been the slightest influence upon his constipation. Nor have any of the usual methods of treating chronic constipation been of service.

CASE III

Male E. Weight, 218 pounds. Height, 6 feet $1\frac{1}{2}$ inches.
Age, thirty-seven.

Chief Complaint—"Nagging affair in here" (pointing to his right groin) Doctor told him a chronic appendix Also more or less trouble with intestines Some constipation tendency

He has depressed fits, thinks everything is wrong, and a sort of apprehension—fear of impending troubles—these occur at irregular intervals, he is dizzy with them—no headaches As a boy had many "sick headaches" between ages of eleven and twenty

Patient was a thin boy, grew 6 inches in his fourteenth year Long and thin Impacted wisdom teeth Began to put on weight at twenty, changed his type then Married at twenty-four years and gained more weight promptly

As a boy he noticed at the age of eleven that his right testis was lacking Thinks size of genitalia is below average Libido average, potentia rapid Married twelve years, no children Examination of semen two to three years ago revealed inactive spermatozoa

Bowels always have tendency to constipation Notices some days when he has urinary frequency No cardiac or respiratory sensations Fatigued rather easily by nerve strain Physical exercise makes him feel well

Measles and mumps at fourteen, both sides and also in the one testicle (This preceded his sudden growth N B, Was the one active gonad destroyed and so with its influence removed, the pituitary stimulated length growth and subsequently fatigued with weight increase?) Scarlet fever, chicken-pox, no diphtheria, tonsillitis—partial tonsillectomy, no malaria, typhoid, or pneumonia

Patient is not musical Likes sweets Not much ambition Not especially keen about his work, likes to be given a definite job which he understands, then he can go ahead and do it, but if he gets up against a new thing which he doesn't understand he gets nervous and fidgety

Dreams that he has gotten up to his last year in college and then can't get past the final examinations Always gets that far and then can't get past that point This is a repeating dream Rather sluggish, heavy "fat brain"

Physical Examination — Well-developed mons veneris Deep oval cleft at root of penis Small external genitalia Short scrotum Left testicle present, but atrophied Testicular sensation is preserved Right testis is absent from the scrotal sac Just above Poupart's ligament on the right there can be felt in the iliac fossa an elongated oval mass which on pressure feels elastic and tense The patient complains that pressure on this mass produces typical testicular pain Undoubtedly this is the undescended testis and is the structure which accounts for the uncomfortable sensations in this region which have been looked upon as chronic appendicitis

Basal metabolism determination, + 17 per cent

Laboratory Reports

Blood

Sugar, 090 per cent

Urea, 032 per cent

Blood Count

HGB, 80 per cent Talqvist, 85 per cent Sahli

RBC, 5,440,000

WBC, 10,200

Differential

Poly, 63 0 per cent

S L, 30 5 per cent

L L, 5 0 per cent

TR, 1 5 per cent

Red blood-cells fairly normal in size and shape

Slight anisocytosis

Urine (10 30 A M specimen)

Total amount, 180 c c

Color, clear amber

Reaction, acid

Specific gravity, 1 030

Sugar, None

Acetone, None

Albumin, None

Indican, +

Misc Occasional epith

Glucose Tolerance Test

Urine	before glucose,	Sugar
	one hour after glucose,	Sugar
	two hours after glucose,	Sugar
Blood	one hour after glucose,	Sugar 103
	two hours after glucose,	Sugar 069

x-Ray of Head—The radiograph examination of the head shows a skull evidently of the mesocephalic variety, having a normal calvarium both in thickness and contour. There is no evidence of increased intracranial pressure. The posterior occipital protuberance is somewhat prominent.

There is a slight area of calcification in the ligmentum nuchæ, slightly separated from the protuberance. There is no separation of the sutures. The sella is small and almost completely closed in. The floor is clear cut and shows no evidence of erosion. The dorsum has a rather heavy tip. The ethmoid cells are clear.

The entire examination, aside from the small sella, which is in this case perhaps of little significance, shows no evidence of intracranial pathology.

The radiographic examination of the hands shows a few quite small spicules about some of the joints. Most marked in the first joint of the right thumb and the terminal joint of the right small finger. The bones themselves show no abnormality. The tufting of the terminal phalanges is perhaps slightly more pronounced than is normally seen.

Summary—This patient presents a very interesting picture of an individual who started out with a genital tract developmental fault. At the age of fourteen an attack of mumps destroyed the descended left testicle. During the year following this attack the patient grew 6 inches in length. While the external genitalia are small in development the secondary sex characteristics are largely of the reverse type in the anatomic pannel. It is interesting that the psyche and the sex eroticism is of the masculine type and active. It is highly probable that the interstitial portion of the undescended testis is adequate.

It will probably be unwise to interfere with the undescended testis surgically

Discussion—This patient is almost a successful male individual From the point of view of his anatomy, however, he

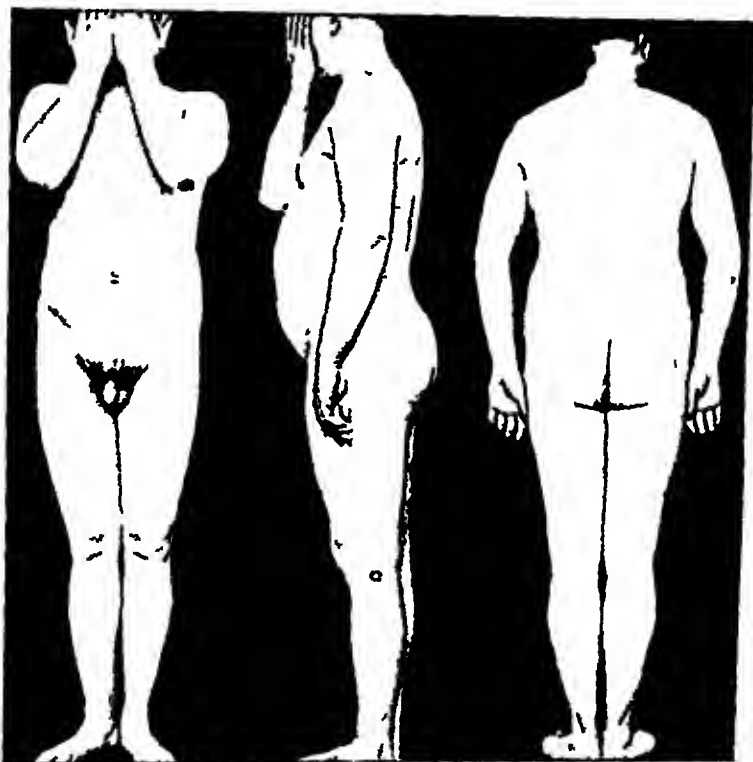


Fig 139—Case III Observe the much greater straightness of line than that found in Cases I and II, much more vigorous position in standing, and masculine curve of the hand Also observe hair on inside of thigh running into the groin **Diagnosis** Left testicular atrophy Right cryptorchidism

presents characteristics of a similar though less extreme nature to those seen in Cases I and II

He is above the average height, the extremities are greater in length than the trunk, and the pelvis approaches the shoulders in width Furthermore, there is a superabundance of fat dis-

posed along lines similar to those of Cases I and II, but less sharply localized. It is more a general increase of subcuta-

[illegible]

Fe 140—Case III

Now Case III is of peculiar interest because the striking

secondary sex characteristics—the voice, facial hair, mental vigor, masculine psyche, muscular strength, and male sex eroticism—are all present. This is so notwithstanding the fact that the individual has serious gonadal faults. In the first place, he was born with a congenitally undescended testis on the right, and, in the second place, at the age of fourteen an attack of mumps completely destroyed the left descended testicle. During the year following the attack of mumps the boy grew over 6 inches in height. In this phenomenon there is an analogy to the length growth of the castrate.

It is accepted as the result of experimental and clinical observation that the pituitary gland increases in size and activity following removal of gonadal influence, and so we see in the circumstances of rapid growth following the attack of mumps an analogous phenomenon. In the case of the castrate, however, there is, in addition to the length growth, the complete absence of secondary characteristics. But in this patient there was an undescended testicle which escaped the mumps infection. This gland can be felt easily in the right flank, and unquestionably has saved its bearer in precisely the same way that the successful testicular transplant does in the experimental animal castrate.

It is interesting to observe that in all these 3 cases—notwithstanding the general heaviness of build and breadth of face—the palatal arch in each individual is high and narrow and that the dental arch is a very narrow or pointed oval. In Case I the teeth are absent, so that their arrangement cannot be described, in Case II close set and even, but in Case III there is a congenital absence of both lateral incisors. Some recent authors have maintained that absence or irregularity of the lateral incisors is always associated with a gonadal fault. Such a generalization is not justified at present. Yet there are very many individuals in whom the two phenomena are present.

All 3 of these cases present great similarities in habitus and all present certain gonadal faults. All have, besides, characteristics which are analogous to many changes found in the acromegalic. All three, furthermore, show a well-marked

white line of Sergeant While there is no definite proof of the significance of this line, it is generally accepted at present as indicating an insufficiency of the adrenal glands This phenomenon will be referred to again in connection with Case IV

CASE IV

Chief Complaints—Pain in the upper epigastrium and lower abdomen for a year, character, burning, continuous, no variation, no relation to meals, nauseated, but no vomiting with the pain Previously before pain began she used to vomit three to four times daily Vomitus never bloody

About two months ago she began to have pains in the lower abdomen, most marked in the suprapubic regions, and burning on voiding urine She had hematuria for a month about five months ago, then dysuria, nocturia, and general frequency

Has lost 27 pounds in the past year, fatigues easily and feels weak

No previous serious illness, no operations, no respiratory or cardiac symptoms Always constipated

Skin has become darker in past year and a half The hair on face and body began two years ago, has always had hair on arms

Married No children, one pregnancy, miscarriage from strain at laundry work

Menstruation began at nineteen years of age At first, very irregular, three to six months interval, duration of each period, one week, no pain Miscarried at two and one-half months Married second time seven years ago Intercourse normal

Physical Examination—A pumpled hairy, oily skinned, middle-aged woman Marked tremor of extremities, and often of head and body Mask-like face

Eyes Pupils not regular, react normally, irises of different color Fundi normal

Mouth Tongue coated and tremulous Teeth, pyorrhea Tonsils, small, reddish

Heart and lungs negative Blood-pressure 148 systolic

Abdomen In each flank, deeply placed in the kidney region,

there is felt a small hard tumor which slips easily under the fingers, too deeply placed to be accurately defined

Reflexes Tendon reflexes everywhere markedly exaggerated

Pelvis Introitus admits two fingers, no tenderness in fornices Uterus small, round, in midline and anteфлекed Cervix long, moderately hard, no masses, moderate leukorrhea

Bladder Cystoscopy negative Some bright blood with urine from right ureter Examination for t b c negative

Kidney function Pthalein, 65 per cent Blood urea, 0.35 gm Blood CO₂, 45.3 vol per cent, 57.6 vol per cent

Blood count Hemoglobin, 85 per cent, red blood-cells, 5,260,000, polynuclears, 83.5 per cent, small lymphocytes, 10.5 per cent, large lymphocytes, 2 per cent, large mononuclears, 2 per cent, eosinophils, 0, basophils, 1, transitionals, 1

Stools negative

Gastric fasting expression and serial test-meal

	Fasting	One-half hour	One hour	One hour and a half	Two hours
Free HCl	0	12	28	60	62
Total acidity	18	52	58	64	66
Lactic acid	0				

Guaiac Streak of gross blood, probably traumatic

Microscopic Negative

x-Ray of kidneys Shows nothing

x-Ray of sella There is some vagueness and irregularity of dorsum and floor of sella, which is itself of rather large size

Basal metabolism +6

Sugar tolerance test

Time	Blood sugar	Urine for glucose
Fasting	1.0 gm	0
Two hours	2.5 gm	+++
Four hours		Not obtained
Six hours		+

Evidently a slightly diminished tolerance

Urine Shows occasional faint trace of albumin, no casts

Case IV presents a very striking picture of virilism in the

female The outstanding features of the case are, first of all, the preservation of the infantile trunk extremity relationship, namely, the trunk length greater than the extremity length

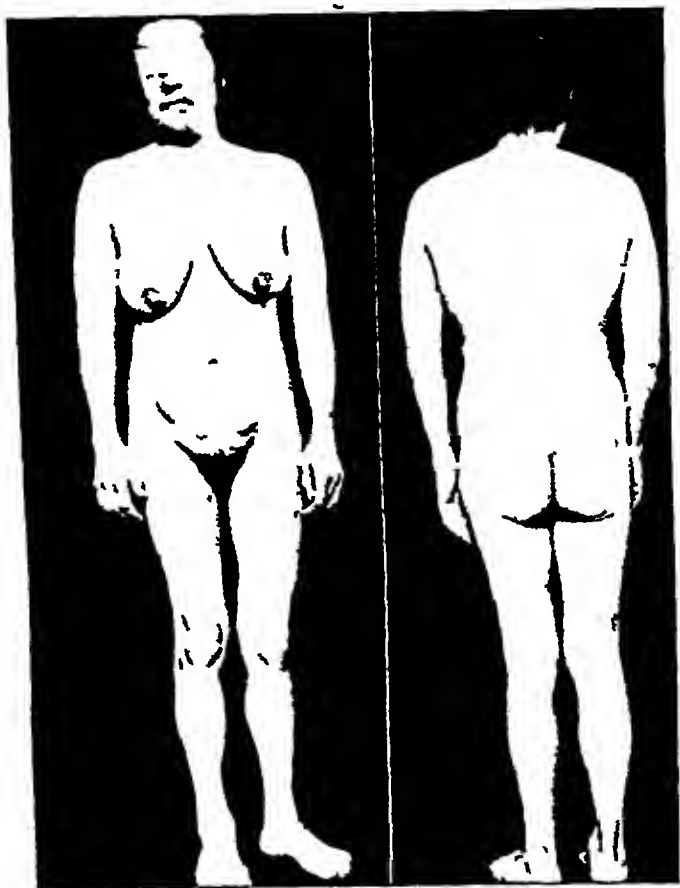


Fig. 141—Case IV Observe enormous breadth of shoulders, narrow hips, and masculine contour of legs Note the hair on thigh, continuous with the pubic mass Also note pigmentation and masculine way of holding hand
Diagnosis Virilism Double adrenal tumors

The shoulder width which is enormous, is much greater than the pelvic width and all the vertical lines of the body tend to straightness rather than to curves

In connection with the trunk extremity ratio it is of interest to call attention to the observations of Tandler and Gross in their discussion of the castrate. Just as the reverse ratio is characteristic of early removal of sex gland influence, so also is the ratio of the present case found in association with early sex ripening. These authors point out that women in general arrive at maturity earlier than men, and that, in general, the trunk extremity relationship in women is that of long trunk and



Fig 142 —Case IV Showing growth of hair on the face. Note also the stolid and rather vigorous expression, also maxillary prognathism, and large ear. *Diagnosis: Virilism. Double adrenal tumors.*

short extremities. They further point out that the races inhabiting southern Europe, whose age of sex ripening is characteristically young, preserve this trunk extremity ratio, whereas, the races of northern Europe, in which the sex ripening is later, present the reverse characteristics in association with greater total length.

While the breasts of this patient are of normal female character, the conformation of the extremities, especially of the legs below the knees, is just as characteristically masculine, the

calf being developed more to the inner side of the midline than the outer

NAME E.T. AGE 44 SEX Female NATIONALITY Bohemian

HEAD Shape small, high, narrow

FACE Long, oval, minor region broad

PROFILE Prominent nose, maxillary prognathism.

EYES Deep set, medium

INTERPUPILLARY SPACE 55

MOTION: quick, transitions, slight Dasyptile sign

Color Eyes brown, high

PALPEBRAL FISSURE Long-medium short-wide-medium narrow

Color Eyes black

Palpebrae slight puffiness under ridge

SQUINT 0

CLARELLA Not prominent

SUPRAORBITAL RIDGES Not prominent

NOSE Skin-Large-medium-narrow

FORM long, high bridge, pointed.

EARS Skin-Large-medium-narrow

SHAPE

LOBE rather heavy, irregular, short

JAWS Faint Arch-High-set-medium-narrow

DENTAL Arch-broad-medium-narrow

TEETH: Spaced close set

QUALITY fair to good

Color Gray white

Shape Upper sharp, small, lateral

Lower similar to central

Pulp Fairly regular

WEIGHT 160.5 cm.

WEIGHT

ARMS To wrist 183 cm. Shoulders & chest broad and heavy

ARM and fore-arm short (62 cm.)

TRUNK Length 79 cm.

LOWER EXTREMITY Length 78.5

RATIO

HANDS Skin-Large-medium-narrow

FINGERS Flat-to-oval-medium-narrow pointed heavy, long

NAILE large small very small

Shape very oblong

RATIO

SHOULDER Length 37 cm.

PELVIS width 26 cm.

SUB-COSTAL ANGLE 91 deg. medium-narrow

CHEST Another prominent deep, short

ENIFORM Long-medium-narrow

HAIR Body Color black

DISTRIBUTION: very thin, varying on typical masculine baldness.

Forehead line high.

EYEBROWS Sparrow: Wide-medium-narrow and brown-arch-V shape

Thicker medium heavy

Distribution Outer half rather scant

BEARD Heavy growth down in front of ears heavy over upper lip and chin

ANT CHEST: Heavy growth over pectoralis and mid-sternal generalized lumps besides

ABDOEN considerable growth-suprapubic. Very heavy, ascending to umbilicus over rectus

AXILLA heavy

ARMS rather scant

Heavy perical hair

POST TRUNK size of neck, dorsal patches, lumbar, and buttocks

THIGHS heavy, continuous with FOREARMS much heavier

LEGS very heavy, long, and black.

GENITAL SYSTEM no abnormalities

Very oily and coarse general dark tone;

Pigmentation at sites of chronic irritation

MUCOUS MEMBRANE clear

SCROTUM AND VAGINA rather scant

BREASTS Long-medium-narrow

BODY CONTOUR Very boyish, broad shoulders, spindle legs

Straight lines narrow hips;

and modelling of leg held the knee with muscle on the inside of calf is very masculine

Fig 143—Case IV

The excessive hair and its distribution in this individual is another striking feature. The distribution is typically that of the male and the increasing facial hair has already gone beyond

the point so frequently seen in elderly females, and is approaching the true masculine facial growth

A great deal of stress in the discussion of hair distribution is laid upon the suprapubic arrangement as differentiating sharply the male and the female, the transverse upper border of the crines being considered feminine, the pyramidal, masculine. As a matter of fact, there is no such final and sharply marked line of differentiation, the two types of upper margin frequently merging very subtly one upon the other. Another feature of the hirsute arrangements in the region of the crotch which is perhaps more characteristic of the different sexes is that which obtains in the angle of the groin. The typical feminine arrangement presents absence of hair in the groin continuous with the bare thigh, whereas the typical masculine arrangement displays a continuity of the thigh and pubic hair through the angle of the groin.

As far as secondary sex characteristics are concerned, this patient presents the boyish form and the masculine hirsutes. The trunk extremity ratio indicates an early awakening of the gonadal influence. Suspicion was entertained that she might be an example of pseudohermaphroditism. The external genitalia, however, are perfectly molded and the pelvic examination reveals a normal uterus.

There follows another group of phenomena which must be considered in connection with the foregoing, but which does not belong in the category of the secondary sex characteristics. These are (1) pigmentation, (2) the absence of the white line of Sergeant, (3) gastric hyperacidity, (4) muscular weakness and tremor, (5) the tumors in the flanks.

The first four are, in a sense, mutually paradoxical, muscular weakness, pigmentation, and gastric hyperacidity are usually associated with insufficiency of the adrenal gland, for they are to be compared with the classical symptoms of Addison's disease. But the absence of the white line is difficult to explain, unless its absence be associated with the well-sustained blood-pressure. It may be remarked that while the patient complains of muscular weakness, there is an intense vigor in all her emotions as well as

a generalized tremor, which gives the impression of a sthenic state of the whole neuromuscular system

The fifth phenomenon in this group is that of the tumors in the flanks. In 1912 Alfred Gallaix described at length a condition which he termed the "genito-adrenal syndrome." In this communication he reports a number of cases from literature and several from his own observation. The descriptions of his cases and their photographs are extraordinarily like that of this case. As the result of his observations the point is made that there is a sharp distinction to be drawn between pseudohermaphroditism (in which the external genitalia of one sex are found with the internal genital organs of the opposite sex) and the appearance in an individual of one sex of the secondary sex characteristics of the opposite sex. The patient under consideration (Case IV) undoubtedly displays the latter condition. Unquestionably, she possesses congenitally faulty ovarian glands because her menstrual function was delayed until her nineteenth year and never attained regularity. Nevertheless, they were sufficiently developed to permit impregnation and, so far as can be determined, successful gestation up to the second or third month, at which time an abortion resulted from physical strain. She presents, however, late in life secondary sex characteristics of the opposite sex. In association with these secondary sex characteristics are also found signs pointing to disturbance of the adrenal function—the tremor and asthenic muscular state, the maintenance of blood-pressure at a slightly elevated level, and the appearance of pigmentation. The position of the tumors, highly placed and deep in each flank, established the diagnosis almost beyond peradventure.

Speculation as to the mechanism behind the symptomatology of these cases leads at once to a consideration of the association of the adrenal cortex to the genital apparatus. It is well known that in the developing embryo the primitive cell streak which ultimately forms the ducts of Muller and of Wolff, provides also the cells from which springs the adrenal cortex. Embryologically, therefore, the association is close. In most of the cases described by Gallaix there is always a period

of great physical vigor, undoubtedly associated with the early stimulating presence of the cortical tumor. As the cases progress this stimulation phase slides gradually over into one of adrenal failure. These tumors are very much more common in females than in males, and the change in the secondary characteristics is always toward virility. In young males and also in young females these cortical tumors are frequently associated with precocious development and hypergenitalism. This group, of course, includes the well-known instances of the "Infant Hercules."

It must not be supposed, however, that tumors of the adrenal cortex are the only causes of these phenomena. The interesting paper of Guthrie and Emery indicates that similar conditions may be associated with lesions of various other members of the endocrine group.

The following case is presented to illustrate this point.

CASE V

F J Age forty Occupation housewife

Chief Complaint—Pain and gas on stomach Duration two years

Family History—Mother had weak heart, had stroke, died. Father died of meningitis. Four sisters living, two died in infancy.

Personal History—Weight, two years ago, 190 pounds. Weight now, 170 pounds. Sleep poor. Appetite good. Bowels move one to four times a day. Has occasional diarrhea. Urination daily five or six times, night, none or once.

Past Illness—Measles and scarlet fever. Accidents, none. Operations, none. Children, none. Miscarriages, none.

Patient was a very small, thin child—at age of twenty-three began to get fat. Married twice, first time at twenty-two, before she was fat. Second time, six years ago. Never pregnant.

Periods began just before fourteenth year. Never regular—three to four months' intervals. At age of twenty-two very scant and seldom. Now for past six months, under treatment, has been menstruating more regularly—every month.

Has gas—bowels tend to constipation now

Has had hair on face since eighteenth year—increasing Had measles, much tonsillitis, no diphtheria, no scarlet fever, thinks she had the mumps

Patient is strong muscularly, but tires easily She is very sleepy much of the time

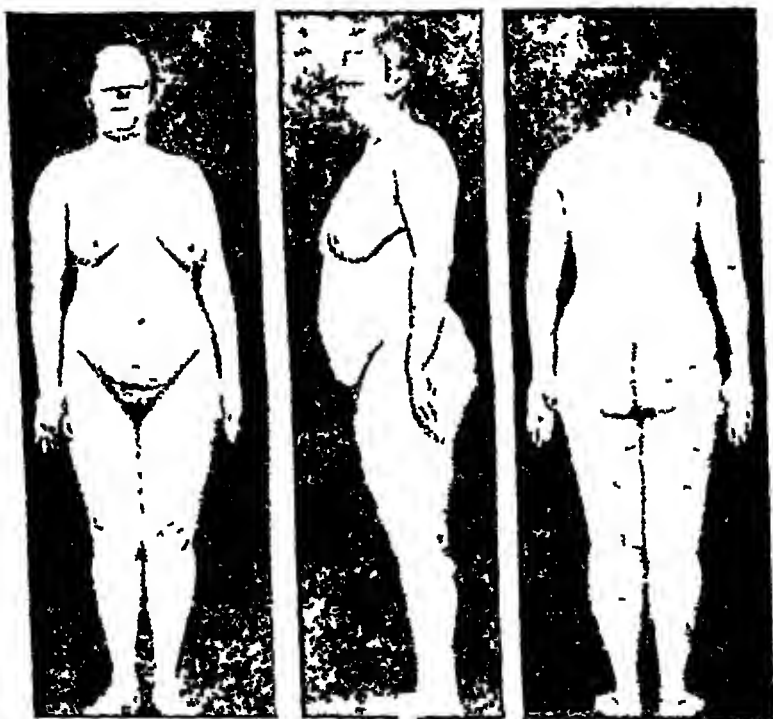


Fig 144—Case V Showing the extensive growth of hair and the adiposity of the neutral type, yet still retaining certain basic feminine curves
Diagnosis Virilism Ovarian tumor?

Has burning and itching of skin and in stomach

Psyche is extraordinary Like a boy No suggestion of modesty in disrobing

Present Illness—For past two years patient has suffered with gas on her stomach and occasional pain across her abdo-

men Passes a great deal of gas, with occasional sharp cutting pain Has occasional feeling of nausea and yesterday and today raised a white slime Patient also has occasional diarrhea Has occasional burning sensation in urination For past week has had tenderness in region of epigastrium

Discussion—This case presents many similarities to Case IV The male secondary sex characteristics are strongly developed, especially in the modeling of the face, the expression of



Fig 145—Case V Observe that the caption to Case IV applies to the face of this individual Observe also the vigorous line of the shoulder, present likewise in Case IV Note also the very pronounced maxillary prognathism and nasalization Diagnosis Virilism Ovarian tumor?

the countenance, and the distribution of hair Even more marked than in Case IV is the virilism of this patient's psyche, which resembles that of a boy It is interesting also that this patient has an absent lateral incisor tooth, and attention is called to the remarks on this point made under Case III

Her menstrual function has always been very irregular Though it began at fourteen years of age, it was never regular and often ceased entirely for periods of three to six months Case IV had a somewhat similar menstrual history, except that

in that instance the function did not begin until nineteen years of age, and for the first few years was equally irregular, with long intervals

AGE 21 SEX Male NATIONALITY German Jew

HEAD: Face - "Egg-shaped" and high

FACE Oval PROFILE Military physiognomy

EYES Deep-set, blue INTERPUPILLARY SPACE 35

E - 14 and 16 NOSE

Color - Dark Gray PALPEBRAL FISSURE

Odor 0

NOSE

GLABELLA - Between eyebrows SUPRA ORBITAL RIDGES ++

NOSE Bridge - straight and strong FORM

FAIR Skin - fair and smooth SHAP

LOFT. Large and square

JAW P - strong - H - fair and strong DENTAL Arch - low - medium - symmetrical

TEETH Strong About 16 normal incisors QUALITY

Shore COLOR

Pinkish

HEIGHT 157 cm WEIGHT

ARMS Upper 1.5 cm

TRUNK Length 80 LOWER EXTREMITY Length 83

HAIR Fair - light brown FINGERS Fair - medium pointed

to be fair in all NAILS Small fairly well covered.

SHOULDER Square PELVIS Wide RATIO

CHEST Average pointed form CHEST

HAIR Body Color Brown DISTRIBUTION Scattered high - several red streaks

EYES BROWN Intense Wide-set - medium - in between - all in "W", heavy - bushy

Thick

Dark brown

FEARS Empty mouth and throat

ANT CHEST Small hair and circumcised

AP ROMP. Can move SUPRAPUBIC

to 2 cm - medium down to 2 cm - also thighs heavily haired and legs

AVOID Heavy ARMS Fairly haired

POV TRUNK

TH GHS FOREARMS Heavily haired

LC

CRANIAL SYSTEM In cranial part of body large - especially behind ears - occipital small

to 2 cm - all pointed - small - in part of body - to 2 cm - large - all in

ML COLE MEMBRANE

S' P' L' AND S' FAT

BOY CONTROLS

Blood Pressure 144/70

to 2 cm - all

Fig 146—Case V

The external genitalia of Case V shows an unusual hypertrophy of the labia minora, and rather a large clitoris. The cervix is very small and pointed and the uterus sharply anti-

flewed Just above the pubic bone a large mass about the size of an orange can be felt, which seems to be connected with the uterus. The question arises, Is this example of virilism in the female due to a similar cause as that found in Case III? The literature contains examples of the phenomenon of virilism associated with ovarian tumors as well as with cortical adrenal tumors. In Case IV masses were felt in each flank, in Case V a mass in the pelvis. Both these cases present anatomic characteristics of the male type—Case IV both in the face and body—Case V chiefly in the head and face. Furthermore, Case V has the added feature of adiposity with the fat distribution of the neutral type discussed under Case II.

The patient comes in complaining of "pain and gas of the stomach" for the duration of two years and an increasing tendency to constipation. Are these symptoms the expression of a faulty physiology having a common causative factor, with the reverse secondary sex characteristics? So far only are we justified in going with this case with the findings at hand.

GENERAL CONCLUSIONS

In the presence of extreme disturbance of function of certain individual representatives of the endocrine glandular system there exist definite anatomic, physiologic, and psychologic characteristics. These characteristics, as described, have been so frequently associated with the partial absence or insufficiency of the same gland or glands that we are forced to the conclusion that the glandular faults are responsible for the altered state of the individual.

There are two distinct aspects of this subject which we may consider, and each well may form the purpose of careful study. The first of these is the investigation of the cases themselves for their own intrinsic interest, the second opens up or, perhaps rather, illumines a very old problem, namely, that of constitution in medicine. The attempts of Laycock, Addison, and Hutchinson to classify mankind into types was largely unsuccessful because of the lack of a normal standard. With the increase of our knowledge of the glands of internal secretion these ac-

cepted endocrinopathic types have become so definite, so easily recognizable, and so constant in their manifestations that they provide a standard. It is of no significance in any scientific method which depends upon comparison and analogy what the standard is—whether it be normal or pathologic—so long as it be constant in both cause and effect. Consequently, these cases provide a reliable pathologic standard with which to compare other individuals presenting similar though less well-marked characteristics. It remains for the clinician so to refine his observations of human anthropologic markings that he may see in each curve of outline, each irregularity of dentition or displacement of fat, slight pigmentary markings, or change in bony modeling, analogy to one or other of the known and accepted endocrinopathic types.

Similar refinements of observation must be carried into the fields of physiology, psychology, and doubtless also immunity, and similar comparisons made with these attributes of the endocrinopath. It is only by this means that we shall reach the point of knowing just how much and what the glands of internal secretion have to do with the determination of an individual constitution. We are only just at the threshold of this difficult and important subject, and at this stage the development of reliable methods of investigation and sound habits of interpretation are sadly needed for its elucidation. Unfortunately, the nature of the problem seems to be such as to encourage the bad habit of "pyramiding" hypotheses.

This has produced the present tendency to inject into the study of normal and disturbed phenomena of growth, development, and bodily form and function a new and rather mysterious and fanciful specialty called "endocrinology." The unfortunate lack of balance and unwise consideration of evidence which many so-called endocrinologists have displayed in the flood of recent literature bids fair to drive into disrepute, for a time at least, a serious consideration of the great importance to medicine of the glands of internal secretion. Obviously the enthusiasm for this subject springs from the basic desire of physicians to gain more understanding of individual human constitution.

From the earliest days this potent factor in disease has been perceived by clinicians, and great personal skill in its recognition was achieved by many of them. But this skill was more the result of experienced intuition than of precise method. The present-day "endocrinologist" is merely reverting to the former.

Now it appears that bodily form and function, the constitution of the organism, are closely related if not actually dependent upon the activities of the endocrine glands. Furthermore, precise methods of investigating some of the capacities of various members of this glandular group have been developed. These are fortunate additions to the physician's armamentarium. Logically, they should be used by him as are all other methods gathered at the bedside or borrowed from the laboratories of pure science. Yet the fascination and novelty of this subject is such that it fires the imagination and the poetry of men's souls more than the reason of their minds. Endocrinology is properly but a phase of general physiology, and as such should not be set apart as a special subject dominating all medical thought and action. Knowledge of the functions of the individual glands and their interrelationship is of great help toward understanding the factor of constitution in disease. It is as a means to this end that the study of endocrine function is properly related to medicine, and not as a specialty of medicine.

CLINIC OF DR H RAWLE GEYELIN

PRESBYTERIAN HOSPITAL

THE SIGNIFICANCE OF GLYCOSURIA

THE significance of glycosuria when accompanied by other clinical symptoms of diabetes is simply confirmatory evidence of an obvious condition. The prognosis is, as you all know, variable, depending chiefly upon the age of the patient at the time of onset, and, more rarely, irrespective of the age, depending upon the individual peculiarities of the disease.

There are other conditions, probably much more frequent than has hitherto been supposed, where the significance of the presence of glycosuria is much more problematic, namely, when it is not accompanied by other evidence of diabetes. In these conditions the glycosuria is most often discovered accidentally in routine or life insurance examinations. Glycosuria may continue as a constant phenomena or be intermittent in character, and the health of the patient is very little, if at all, impaired. Many of these cases continue to show sugar in the urine for months or years, but, if untreated, I think the majority eventually develop into outspoken cases of diabetes mellitus or, as in other instances less frequently encountered, this glycosuria may continue for many years without the development of diabetes or even loss of weight. This latter form of glycosuria, provided that it meets with other diagnostic requirements which I shall speak of later, is termed "renal glycosuria."

There is still a third form of mild glycosuria which is met with in certain toxic conditions, fevers, etc., but in these conditions the glycosuria is only transitory.

It is my purpose today to present to you several cases which illustrate the difficulties that surround us in trying to determine what diagnostic and prognostic significance is attached to the

symptom, glycosuria first, when it is accompanied by atypical symptoms of diabetes, second, when found as the only presenting symptom

The first case illustrates a rather unusual condition, namely, diabetes with mild onset in a child who apparently has since become a case of renal glycosuria

CASE I

A H, male, age six years Admitted to Presbyterian Hospital November 26, 1911, discharged December 9, 1911 History No 31,327

Chief Complaint—Incontinence of urine and progressive weakness

Present Illness—In July, 1911 the patient first noticed nocturnal polyuria and incontinence About two months later this incontinence and polyuria occurred also during the day Thirst increased and the child grew progressively weaker (No mention is made of loss of weight) Glycosuria (amount unknown) first found by a physician two months before admission to hospital All the symptoms have continued to date

Past History—When ten months old patient suffered from an attack of infantile paralysis Both legs and the right arm are said to have been completely paralyzed There was gradual improvement after two months, but weakness of both extremities has persisted When two years old patient was operated upon and had a tenotomy of both Achilles' tendons The urine was tested for sugar one year ago, and no sugar was found

Family History.—Mother has had diabetes ever since the patient was born Her glycosuria is very slight at the present time There are no other cases of diabetes in the family

Physical Examination—Thin, pale child, markedly deformed, who shows the following significant findings

- 1 Double dropped foot, more marked on the right
- 2 Knee-jerk very sluggish
- 3 No ankle-clonus
- 4 No Babinski
- 5 Double flat-foot

- 6 Marked steppage-gait
- 7 Abnormal pelvic movement when walking
- 8 Movements generally atavic
- 9 Hand grip good and equal in both hands
- 10 General, but slight emaciation
- 11 Marked kyphosis of the lumbar region

Course in Hospital—On an antidiabetic diet with reduction of the COH to about 30 to 50 grams, but with protein and fat kept at a high level, the patient showed 1 per cent or over of sugar in the urine during his entire hospital stay. No acetone or diacetic acid was found. The fermentation test was done on the urine and was positive. From then until his next visit to the hospital dispensary, August 11, 1915, he was not seen, and no examinations of the urine for sugar had been made during that interval.

Readmitted to the Presbyterian Hospital April 25, 1916 for an orthopedic operation. No sugar was found in the urine at that time. Patient was in good health and gaining in weight.

Readmission July 26, 1917, for another orthopedic operation, 12 per cent of sugar found in urine, together with a trace of acetone.

Blood sugar (fasting) eleven days after admission, when the patient was sugar free, showed 0.93 per cent.

The patient was put on a fast as soon as he was admitted to the hospital, and the glycosuria disappeared after one day of fasting. The diet was gradually raised until on August 11th it had reached COH 100, protein, 80, fat, 30. There was no sugar in the urine, but there was still a faint trace of acetone and diacetic acid. His weight was 65 pounds at this time.

From August 21, 1917 until his last admission to the hospital, September 15, 1920, several observations on the urine were made in the surgical follow-up, the results being as follows:

February 26, 1918 Urine glucose = 0 Weight 80 pounds

April 9, 1918 Urine glucose = 0

No examination from that time until June, 1920, when a faint trace of sugar was found in the urine. His weight was 85 pounds at that time.

On the last admission, September 15, 1920, the patient was put on a diet of COH 200, protein, 75, calories 2000. There was a faint trace of sugar in the urine. This diet was rapidly raised within six days to COH 300, and maintained for three weeks. The urine showed faint traces of sugar at intervals, eight times during this later period of observation. The blood sugar (fasting), September 20, 1920, was 0.91 per cent, two hours after glucose 100 grams, 0.96 per cent. There was no glycosuria.

On September 27, 1920, one-half hour after breakfast, the blood sugar was 0.95 per cent.

On October 1, 1920, one-half hour after breakfast, the blood sugar was 1.07 per cent.

On October 5, 1920, half an hour after breakfast, the blood sugar was 0.84 per cent.

On October 14, 1920, half an hour after breakfast, the blood sugar was 1.20 per cent.

During his entire stay in the hospital no acetone or diacetic acid was found in the urine.

In individual specimens of urine taken at the time of the various blood sugar determinations no sugar was ever found.

Quantitative determinations of the sugar in the urine ranged from 1 to 2 per cent. These were on twenty-four-hour specimens.

Weight on admission and on discharge, October 22, 1920, was 95 pounds.

Since discharge from the hospital until January 1, 1921 patient has been on a general diet, and has shown faint traces of sugar in all of the ten examinations that have been made. Nocturnal polyuria has been intermittent, but is now (January, 1921) much less than it was originally.

You will all observe that in this case the onset of glycosuria was accompanied by some of the symptoms of diabetes, but in mild form. When first admitted glycosuria (1 per cent) was present in the urine, but no acetone. Moderate carbohydrate reduction was not successful in diminishing glycosuria, and the patient was discharged from the hospital ten years ago with no symptoms or signs suggestive of diabetes other than glycosuria.

and nocturnal incontinence It is unfortunate that no estimations of the blood sugar were obtained during the original hospital admission particularly in view of the subsequent developments The history of glycosuria from 1911 until 1917 is rather inadequate, and in fact, from 1917 up to the present time we know little of the frequency with which glycosuria has occurred

You will notice that at the present time the patient is able to tolerate large amounts of carbohydrate on a mixed diet, while sugar, in traces only, appears in the urine, and these traces of sugar are not constant The blood-sugar is always well within normal limits, in fact, the peak reached in the alimentary curve is much below that often seen in normal individuals without glycosuria The frequency with which sugar is found in the urine of this patient is presumably not increasing, even though this point has not been properly controlled In view of the patient's continued growth and gain in weight it seems probable that the diabetic (if it be diabetic) condition is gradually disappearing

What condition are we dealing with? Does this patient belong to that very rare group of "cured" diabetics? or should he be considered as a mild case of diabetes originally which has developed into a case of "transitory renal glycosuria"?

One must admit that according to the criteria generally accepted as necessary for the diagnosis of renal glycosuria this patient at the present time more nearly conforms to the latter group than to the former or diabetic group

The case is particularly noteworthy in that symptoms of diabetes and glycosuria developed at a time in life when glycosuria is almost invariably associated with a form of diabetes that is very severe and nearly always fatal even if the early symptoms be mild

CASE II

S S female age twenty-two years, single Laboratory worker History number not given Vanderbilt Clinic First seen September, 1919

Chief Complaints —Weakness, loss of weight glycosuria

Present Illness—This is best told in the patient's own language, as follows "At the beginning of December, 1918, I occasionally had short dizzy spells which lasted for a few minutes On the advice of an oculist I examined my urine, but found it perfectly normal Later it was discovered that pus had collected in my sinuses They were pumped and the dizzy spells disappeared About February, 1919 I began to feel unusually tired at the end of my day's work, but as I had no definite symptoms of any kind I did not consult a physician I went away for Easter week, but did not feel rested when I returned I could barely complete my day's work I had no appetite and had lost 15 pounds from September, 1918 to date In the last week of April, 1919 I examined my urine and discovered about $\frac{1}{2}$ per cent sugar I had never had either excessive thirst or excessive urination The total twenty-four-hour urination was greatly decreased or just a minimum normal When I felt particularly tired my skin would itch in small white patches, generally on my arm or back I had noticed this for several years, but had been told that it was just an evidence of exhaustion

"At the time I first discovered sugar my diet included meat or fish once a day, vegetables, fruit, milk, and a small amount of bread I usually ate for breakfast a small dish of cereal, a glass of milk, and sometimes two eggs I ate candy, cake, and other sweets only on rare occasions, possibly only once a month

"When I discovered sugar I immediately dropped bread, milk, and starchy vegetables from my diet, but I did not consult a physician until May 29th By this time sugar had increased to a little over 1 per cent I had lost 20 pounds from my original weight, and my tiredness was not relieved The physician I consulted directed me to continue the diet I had prescribed for myself, with the addition of more fat After this addition the slight trace of acetone, which had appeared at the end of May, disappeared I never, so far as I know, showed any diacetic acid

"A blood sugar taken in June was 89 mg, one in July was 110 mg per 100 c c

"From the time I dropped the forbidden articles from my diet until I came under your care in September I did not have one sugar-free day. The amount of sugar was decreased by the diet, but it never disappeared."

Past History—Patient had a nervous breakdown in 1915, has always tired easily and is of a very emotional disposition. Otherwise the past history is unimportant.

Family History.—Negative for diabetes.

Physical Examination—Well-nourished, dark-complexioned, healthy looking girl, 5 feet in height and about 20 pounds underweight. Otherwise negative.

Course While Under Observation—Patient was put immediately on a very low diet consisting of COH 30, protein 50, fat 50. On this diet she became sugar free in a few weeks and stayed sugar free for one week. Then, in spite of the fact that the diet was continued as before, she began to show sugar again. In view of the fact that repeated blood sugar determinations and sugar tolerance tests had always shown blood sugar values of below 11 per cent, it was decided to increase the carbohydrate gradually making daily observations of sugar in twenty-four-hour urine specimens (incidentally I should add that this accurate control of the urine and food has continued without missing a day up to the present time, February 1, 1921), and the patient has shown glycosuria persistently, the quantity varying from 1 to 3 per cent daily. There have been occasional periods when the urine has been sugar free. On one occasion when the patient was receiving 200 grams of carbohydrate daily (from October 15 to 28, 1920) the urine was sugar free over this entire period. The patient has been sugar free more often while on a COH intake of under 100 grams than she has been on a diet of over 100 grams COH.

The blood sugar taken at fifteen-minute intervals for an hour and a half after a meal containing 100 grams of carbohydrate showed 108 per cent as the maximum, while during this same period the urine showed 2 per cent sugar.

The patient now (January 17, 1921) weighs 128 pounds and feels perfectly well in every respect, but is still showing sugar

constantly in the urine, the diet at this time being COH 210, protein 80, fat 90, with a blood sugar of 110 per cent (half-hour post lunch) and 1 per cent sugar in the urine

This (Case II) differs from Case I in that the symptoms of diabetes are more open to doubt, loss of weight and weakness being the only evidence that could possibly be urged as symptomatic of diabetes in Case II. The failure to increase glycosuria by increased COH intake is present in both Cases I and II. Both patients have gained in weight while taking increasing quantities of food, and while Case II is stronger and has more power of endurance than formerly, she has not been observed over so long a period as has Case I. Also Case II seems to have a more persistent glycosuria. The chief reason for suspecting that Case II was originally suffering from diabetes is that she lost weight and seemed more ill than does a case of "renal glycosuria." Such reasoning, it may be admitted, is open to argument, and there are other reasons for assuming that she has been a case of renal glycosuria from the beginning, the principal ones being the continued low blood sugar and glycosuria irrespective of diet.

CASE III

W H L, male, age thirty, single Hospital No 47,468
Admission date, September 20, 1920, discharged October 5, 1920

Chief Complaint—Weakness

Present History—Four years ago (November 10, 1916) the patient was refused for life insurance because of sugar in the urine. Two weeks following this examination several specimens of urine were tested and, according to the patient's statement, no sugar was found. He continued to eat anything he pleased up to June, 1920. Early in 1918 sugar was found in the urine on several occasions, but the patient was enrolled in the army in August, 1918 and apparently was free from sugar then.

In October, 1918, after an operation for hemorrhoids, polyuria, polydyspnea, and polyphagia were noticed, but no attention was paid to these symptoms, and except for the fact that the

patient was a little less capable of performing prolonged physical work there was no other change in his condition. He was discharged from the army January 1, 1920, and from then on began to lose weight and strength rapidly. On June 1, 1920 sugar was found in the urine (8 per cent). His average weight of 158 pounds, which he had held until January 1, 1920, had fallen to 125 pounds on June 1, 1920. The patient was under moderate carbohydrate restriction from June 1 to September 16, 1920.

Course While Under Treatment—When the patient came under observation September 16, 1920 an individual specimen of urine showed large amounts of sugar, no acetone or diacetic acid. While he has been under treatment and up until December 21, 1920 he has steadily gained in weight and strength on a diet of COH 100, protein 110 fat 130. He now weighs 130 pounds and the blood sugar is 142 per cent two hours after lunch. The patient is carefully weighing all his food and is testing his urine daily for sugar, and is actively engaged in the bond business.

Past History—Negative

Family History—Negative for diabetes

Physical Examination—Except for emaciation it is altogether negative. This patient illustrates a type of glycosuria which in its early stages may well be mistaken for either the transitory type or a renal type but which subsequently developed into a case of moderately severe diabetes. This history and the subsequent development of frank diabetes is, as already indicated, of much more common occurrence than is "renal glycosuria," and is also more common than that type of glycosuria seen in the first patient. One naturally speculates as to what would have happened had the diet been restricted in carbohydrate as soon as sugar was discovered. Also, was the blood-sugar curve typical of diabetes or typical of "renal glycosuria" at the time that the glycosuria was first discovered? This, in turn introduces the question as to what prognostic significance is attached to the alimentary blood-sugar curve in mild glycosuria? Does an essentially normal curve with glycosuria

preclude the future development of diabetes? We will discuss this later

Mr P, what is your opinion as to the ultimate prognosis in this patient?

Mr P In view of the present food tolerance and in spite of the severity of diabetes usually seen during this decade of life, I should think that under appropriate treatment his life could be prolonged for several years

H R G Yes, that is probably true, but is the outlook for a complete recovery good?

Mr P No, I think not

H R G That is correct Even under the most favorable conditions of modern treatment it is doubtful whether this patient will survive for another five years, and should he do so it will be only under conditions of marked invalidism As an illustration of what has happened in this case, I have in mind another patient in whom sugar was found at the age of twenty-two This was four years ago, and although there were no clinical symptoms of diabetes at the time, and although his carbohydrate tolerance was 250 grams during the first hospital stay, he has steadily lost tolerance for food in spite of the fact that he has adhered religiously to a proper dietary and has been continuously kept from sugar in the urine He had, however, a high blood sugar, with slight glycosuria at the time of onset

CASE IV

S L K, male, age thirty-five years, married Hospital No 43,475 Admitted October 1, 1919, discharged October 8, 1919

Chief Complaint—Diabetes

Present Illness—In January, 1916 patient suffered from a nervous breakdown due to overwork He took a "rest cure" for four weeks, and at the end of that time felt perfectly well At that time he suffered from great worry and shock due to the fact that his wife miscarried and was very ill on a railroad train He was in fairly good health, but was excessively nervous from then until December, 1917, at which time a doctor found patient

showing sugar in the urine (2 per cent) At this time he weighed 147 pounds

He continued to show sugar in traces only until March, 1918 He was then put on a very low diet for four weeks, but never became sugar free until July 1918 Patient continued sugar free through July, August and September He attributes this freedom from sugar to the fact that his mind was relieved by the birth of a son

In October, 1918 he began to worry about the influenza epidemic and his glycosuria returned In December 1918 he had influenza, and sugar was constantly present in the urine (1 per cent) This has persisted until the present time (October 1, 1919) During all of this time he had lost 13 pounds, his present weight being 134 pounds From time of onset until March, 1918 the patient ate "any and everything" From April, 1918 until October, 1919 the patient has abstained from abundance of COH and sugar

Past History—Unimportant except that early in 1916 patient weighed 151 pounds, which was his highest weight

Family History—No diabetes Patient's father "suffered from many nervous breakdowns"

Physical Examination—Rather pale blond, stocky, well-muscled young man, of an apprehensive disposition Height 5 feet, 7 inches Slight tremor of the hands and of the upper eyelids when the eyes are closed Otherwise his physical examination is negative

Course in the Hospital—On October 2, 1919 patient was put on a diet of COH 300, protein 100, fat 100, and the diet was rapidly raised to 476 grams COH on October 6th The twenty-four-hour urine, which was examined daily showed 1 per cent. sugar in every specimen

On October 2d the blood sugar was 072 per cent fasting, fifteen minutes after 100 grams of glucose it was 076 per cent Two hours after glucose the blood sugar showed 072 per cent

At this time, the patient being anxious to return to his home in the West, and being particularly apprehensive about the presence of glycosuria, he was advised to eat as he pleased and

not test his urine for one year. He returned for observation September 7, 1920, weighing 146 pounds, and still showing sugar in the urine. Twenty-four-hour specimens on September 7th, 9th, 11th, 13th all showed from 1 to 2 per cent sugar.

On September 9, 1920 the fasting blood sugar was 112 per cent, he then received 100 grams of glucose. The blood sugar one-half hour after this was 138 per cent, two hours after it was 108 per cent. Individual specimens of urine taken during this period showed well-marked reactions for sugar with Benedict's solution. The fermentation test was positive and typical. Glucosazone crystals were found.

Another blood-sugar test taken one-half hour after an ordinary breakfast on September 13, 1920 showed 104 per cent, with sugar ++ in the individual specimen of urine voided at that time.

February 1, 1921 Patient's health is excellent. He has been eating everything he pleases, including sugar, and is much less apprehensive concerning his condition. He still shows small amounts of sugar in the urine.

CASE V

F M, female, age thirty years, single. Occupation clerk. History No 38,899. Date of admission, August 10, 1918, discharged October 17, 1918.

Chief Complaint—Swelling and pain in the right knee-joint of three days' duration.

Present Illness—Six weeks ago the patient fell and injured her right knee. A bruise appeared, and a few days later she noticed pain in her knee when walking upstairs. A week later stiffness and swelling were noticed, the swelling was gradually reduced to half its original size on admission to the hospital. She has had no fever, but she has had slight sore throat, which she says has been present for the past three months.

Past History—For the past three or four years the patient has had swelling of the right ankle. Did not have this last winter. Seven years ago patient had a cough, which lasted for four years. Her physician told her that this cough was due to

her tonsils She has never had a tonsillectomy Except for the loss of 5 pounds during the last two weeks she has not lost weight

Family History—Unimportant, and negative for diabetes

Physical Examination—A well-nourished young woman who presents no abnormality except several white spots on both tonsils The right knee is swollen above and to the right of the patella No redness, no tenderness Pain upon extensive flexion x-Ray of the knee-joint is negative Temperature 100.2° F, pulse 100, respirations 24 on admission

Course in the Hospital—Patient continued to have very slight temperature for five days, but this subsided and remained absent during the rest of her ten-week stay in the hospital The knee also returned to its normal size

The urine of August 17th showed a faint trace of sugar with the patient on a normal diet This was treated by one day's fast which caused the sugar to disappear During the next six weeks while the carbohydrate tolerance was being gradually increased to 300 grams, the patient showed faint traces of sugar in the urine on four different occasions There was no more sugar present when on 300 grams than there had been on 95 grams of carbohydrate Her weight was reduced from 99 pounds on admission to 91 pounds one month later She weighed 100 pounds when discharged

Since the patient's discharge from the hospital she has steadily gained in weight until now (February 9 1921) she weighs 118 pounds An attempt has been made to eliminate the sugar which has been constantly present in the urine and after two or three weeks of extreme carbohydrate withdrawal it has been possible to render the urine sugar free However on resuming a general diet she has continued to show sugar The amount in a twenty-four-hour specimen varies from 1 to 1.9 per cent The fermentation test is positive

While the patient was in the hospital four determinations of the blood sugar were made, and at no time did it exceed 105 per cent Since her discharge she has returned to the dispensary on an average of once per month Blood sugar which

has been frequently taken, has never exceeded 13 per cent except on one occasion, when it reached 16 per cent forty minutes after lunch. This was on November 10, 1920. Glycosuria has been present in all individual urine specimens taken at the time of the blood-sugar determinations.

These last two patients illustrate very aptly the fact that glycosuria, without hyperglycemia, without any clinical symptoms of diabetes, and irrespective of carbohydrate intake, may continue for some years without impairing the health of the patient and without diabetes. The criteria that are now pretty generally accepted as being diagnostic of "renal glycosuria," so called, are the following:

- 1 Continuous or intermittent glycosuria, more or less independent of carbohydrate intake, the percentage amount of sugar appearing in the urine varying from mere traces to as high as 2 to 5 per cent.

- 2 Glycemia which never exceeds the normal percentage concentration, and which in most instances never reaches the highest figures found in the alimentary blood-sugar curve of the normal individual.

- 3 Absence of other symptoms of diabetes continued over a period of years without dietary restrictions.

In adopting the blood-sugar curve—*i. e.*, the blood-sugar values (before, one-half hour, and two hours after standard doses of glucose) as a method of determining the final outcome of a case showing glycosuria without symptoms of diabetes—we must first be familiar with the so-called "blood-sugar curve" in normal individuals. With this test, as well as with other clinical tests when the normal individual is used as a control, we must not forget that it is always important to determine what constitutes a normal individual. This is sometimes difficult when trying to evaluate the blood-sugar curve, particularly in certain people who otherwise would be designated as normal. The blood-sugar curve in normal people will show such abnormalities as the following: (1) a high peak, higher than 18 per cent without glycosuria, (2) glycosuria slight without a rise above the normal in blood sugar, (3) no glycosuria, but a

high and prolonged curve A few people showing one or another of these abnormalities have been noted by various observers, and although in most of these instances no further observations have been made, yet there are a few cases in which continued observation has not led to any conclusion that these persons were potential cases of diabetes or even cases of "renal glycosuria" They should probably be classified as normal people with transitory hyperglycemia or glycosuria It is important to know that there are such people, and possibly these abnormal glycemie curves are indicative of endocrine disturbances, but what is more important Will such people eventually develop diabetes? From what little evidence I have collected in observations made over a period of two to three years I am inclined to believe that, generally speaking, they will not

The typically normal blood-sugar curve after 100 grams by mouth should be as follows

- 1 Blood sugar before glucose 07 to 12 per cent
- 2 Blood sugar within an hour after glucose from 13 to 18 per cent, this representing the peak of the curve, and it is usually obtained within the first half-hour
- 3 A return to the fasting level within two to two and a half hours

The curve that is most suggestive of early diabetes (hyperthyroidism being excluded), even when symptoms are absent, is one in which the blood sugar rises to high normal or higher than normal limits and remains high for more than three hours, or at least does not return to the fasting level within that time, while traces of sugar appear in the urine

The curve that is supposedly typical of "renal glycosuria" is one that starts at the usual normal or low normal fasting level and that rises to a peak which is not so high as the usual normal peak, returning to the fasting level within two hours and accompanied by sugar in the urine

There are manifold variations of these two types of curves as you may imagine but, broadly speaking, they hold true This method of testing is helpful in diagnosis—probably the

most helpful single clinical test—but we do not believe that it is infallible

We come now to a discussion of the type of glycosuria that is characteristic of diabetes and the type that is characteristic of "renal glycosuria." If in a given case when slight glycosuria exists and by COH withdrawal this glycosuria disappears readily and reappears in increasing amounts as the COH intake is increased, we may feel reasonably certain that we are dealing with a case of diabetes. It is true that the cases we believe to be renal glycosuria may also be rendered sugar free by COH withdrawal, but, as a rule, only when such withdrawal is extreme, as, for instance, on complete fasting. Some cases of renal glycosuria, as is evidenced by Case S. L. K., still maintain a trace of sugar in the urine even after a period of fast days. We have never observed this in early and mild cases of diabetes.

After the patient suffering from renal glycosuria has been rendered sugar free in the urine, the resumption of even a small amount of COH (15 to 50 grams) will usually cause a return of glycosuria, which does not increase in quantity as the COH of the food is increased, whereas in mild diabetes the effect of resuming COH in quantities of from 15 to 50 grams would be to produce glycosuria. In fact, any mild diabetic, in order to be classed as mild, should be able to tolerate 50 grams of COH or more for an indefinite period without showing sugar in the urine, and when the COH is increased sufficiently to cause glycosuria this glycosuria would then increase in quantity, especially if we continue to raise the COH of the diet.

I have limited the discussion of glycosuria in this clinic to a rather restricted field, and we must not forget that it is a symptom found in many other conditions. But even granting that this is true, we should make it a rule never to dismiss it lightly as a symptom. Every patient in whom glycosuria is found should be advised to undergo a period of observation in which blood sugar and urine findings are investigated and the food intake is controlled. The patient should then be advised as to the necessity of having periodic tests of his urine made—at least

once every three months for a long time—and to report any symptoms of ill health immediately. Periodic blood-sugar determinations should also be made according to individual indications. Only in this way can the patient's future health be protected, and, incidentally, as data is thus collected much information will be added to our knowledge of the prognostic significance of glycosuria with or without hyperglycemia.

CLINIC OF DRS BERTRAM J SANGER AND LOUIS BAUMAN

PRESBYTERIAN HOSPITAL

VARIATIONS IN CASES OF HYPERTHYROIDISM FROM A CLINICAL, LABORATORY, AND THERAPEUTIC STANDPOINT

THE fact that all patients with hyperthyroidism do not improve under one type of therapy—medical or surgical—led us to believe that some cases, even though they appeared clinically almost identical, were intrinsically different. With this in mind we undertook some critical studies of the condition in the hope that we might discover group features which would assist in outlining a therapeutic régime. Early in the course of our observations differences were manifest. The following cases are illustrative.

CASE I

E. R. History No 45,056, aged thirty-five, male, white, married, traveling salesman, entered the Presbyterian Hospital on February 17, 1920, complaining of cardiac palpitation, nervousness, and shortness of breath. Family history negative except for one sister who is supposed to have had a goiter. Previous history was essentially negative. Present illness dates back three years when patient first noticed rapid heart action and later developed tremor of hands, excessive sweating, and dyspnea on exertion. Struma had been present for about one year. Some loss of weight had occurred early in the disease, but at the time of admission the patient had regained his normal weight. Tonsillitis had occurred early in the disease, which led the patient to have his tonsils removed. The shortness of breath recently had increased to such an extent that he sought

hospital attention Physical examination showed a well-developed and well-nourished young man weighing 63.6 kilograms and measuring 167.5 cm The skin was moist and flushed The patient appeared somewhat nervous, but was without frank exophthalmos, though the eyes were bright and somewhat staring Joffroy and Moebius signs were present The thyroid gland was diffusely enlarged, but no bruit or thrill could be made out The heart was normal in size and position, its action was irregular in force and rhythm The character of the heart sounds were suggestive of mitral stenosis, but no murmurs were definitely heard There was a fine tremor of the fingers and toes The blood-pressure was 150/80 Physical examination was otherwise negative Blood examination was negative The electrocardiogram showed auricular fibrillation, there was a marked pulse deficit The metabolic rate on admission was 55 per cent above normal The sugar tolerance test (100 grams glucose by mouth) gave an essentially normal response

Fasting blood-sugar	0.094 per cent
15 minutes later	0.13 "
50 minutes later	0.15 "
135 minutes later	0.107 "

A questionable reaction for sugar was present in the urine four hours after the glucose administration

Chemical Study of the Urine—The patient received a creatin-free diet of 2570 calories, this was a 30 per cent increase over the patient's basal requirement

Date	Nitrogen intake	Nitrogen output	Creatinin	Creatin
Feb 20	12.6 gm	13.9 gm	1.72 gm	00 gm
Feb 21	12.6 "	13.9 "	1.71 "	00 "
Feb 22	12.6 "	13.1 "	1.38 "	00 (some urine lost)

The x-ray examination of the heart (6-foot tube) did not show cardiac enlargement, but revealed a shadow suggestive of an enlarged thymus

Under rest in bed and digitalis therapy the pulse deficit

cleared up, although the heart action was still irregular in force and rhythm. On October 23d the basal metabolism was 46 per cent above normal, with a respiratory quotient of 0.72.

The patient was discharged on March 6th much improved symptomatically, but with his heart still fibrillating and his metabolic rate still high. After leaving the hospital ambulatory treatment consisted in x-ray therapy. On April 3d after three x-ray treatments the metabolic rate had increased to 53 per cent above normal. On June 23d after six treatments his metabolic rate was still 51 per cent above normal, the pulse was 88 but still irregular, and digitalis was continued. On August 16th after the eighth treatment quite striking changes were manifest. He had felt a steady improvement and finally there has been a disappearance of all of his symptoms—shortness of breath, tremor, nervousness. He had been gaining in weight. On physical examination he now appeared calm there was but a very slight tremor the struma persisted, though somewhat smaller and the heart rate was regular and 84 to the minute. Unfortunately no electrocardiogram was taken at this time, but from the clinical evidence one could feel sure that he was not fibrillating. His basal metabolism had decreased to 8 per cent below the normal. x-Ray and digitalis were now discontinued and on September 25th the patient returned in excellent condition, with a metabolic rate of 6 per cent above normal. He is now back on the road as a traveling salesman and doing his full work without any difficulty.

CASE II

H. G. History No. 26419, aged twenty-two years, male, white a broker by occupation entered the hospital on June 15, 1920 with a history of nervousness, an undue feeling of warmth, exophthalmos and swelling of the neck for the past two years. Family and previous history were essentially negative. The onset of the illness was sudden occurring two years ago when he noticed a swelling of the right side of the neck, nervousness, exophthalmos and a "rush of blood to the head." He was treated with electricity and iodine. He was treated with electricity and iodine. He was treated with electricity and iodine.



with symptomatic improvement, though the gland continued to grow in size. There was no history of ever having lost much weight. He continued, however, at his work, which was that of a curb broker, with very little difficulty, except for some dyspnea on exertion, until he was admitted to the hospital.

Physical examination revealed a fairly well-nourished man with a flushed face, eyes prominent, and lid slits wide. All the corroborative eye signs of Graves' disease were present. The thyroid was diffusely enlarged and a thrill and bruit could be made out over both lobes. The heart was slightly enlarged to the left, the rate rapid but regular. The spleen was just palpable. A fine tremor of fingers and tongue was noted. White blood count 8200, of which 72 per cent were polymorphonuclear. The Wassermann reaction was negative in both antigens. On June 18th the metabolic rate was 55 per cent above normal and the pulse was 104. The sugar tolerance was as follows:

	Blood-sugar	Glucose in urine
Fasting	0.95 per cent	
15 minutes after glucose ingestion	125 "	
60 minutes after glucose ingestion	23 "	
120 minutes after glucose ingestion	23 "	++++
240 minutes after glucose ingestion		+-

The chemical study of the urine gave the following results:

The patient received a creatin-free diet of 3000 calories. As in the previous case, a 30 per cent increase over the patient's basal requirement.

Date	Nitrogen intake.	Nitrogen output.	Creatinin	Creatin	Uric acid
June 29	11.0 gm	13.22 gm	1.038 gm	307 gm	537 gm
June 30	11.9 "	15.39 "	1.20 "	374 "	518 "
July 1	8.4 "	12.47 "	1.046 "	379 "	554 "

On rest in bed and a high calorie diet he improved, but as he became impatient, it was decided that he should go to the country for the summer, eat a high calorie diet, and return in the fall for further observations. The patient was next seen on September 14, 1920, and his metabolic rate was 44 per cent

above normal, in spite of the fact that he had gained weight, felt less nervous, and appeared greatly improved. x -Ray therapy was started. After the third treatment his metabolic rate had fallen to 28 per cent above normal, with striking clinical improvement. At present he has had eight x -ray treatments, his metabolic rate is 9 per cent above normal, he is back at work as a curb broker, and says that he feels entirely well and is able to do this strenuous work without tiring. He sleeps well. His pulse is around 80, and although the struma persists, it is much smaller and feels distinctly softer.

CASE III

M. D. History No 36,148, aged twenty-eight, female, housewife, entered the hospital on September 25, 1917, readmitted on January 8, 1918, and August 5, 1918, for conditions other than the present illness (operations for incomplete abortion, lues). At that time there was no suggestion of thyroid disease. A note in the history of the third admission distinctly states that no enlargement of the thyroid existed and there were neither signs nor symptoms pointing to this condition, except a slight acceleration of the pulse-rate. The patient was seen in the follow-up clinic off and on between admissions, where she was treated for lues, etc. On March 24, 1919 it was noted that she was becoming nervous, and on April 7, 1919 that she perspired easily and that she had exophthalmos, struma and tremor. A diagnosis of exophthalmic goiter was made and the patient was readmitted to the hospital. On the fourth admission, April 12, 1919, the patient complained of fatigability, headache, nervousness, sweating, enlargement of the neck, and swelling of the feet and legs. She had lost 12 pounds during three weeks before admission—present weight 122 pounds.

Physical examination showed exophthalmos and correlated eye signs, tremor of the fingers, tachycardia, and swelling of the feet. White blood count 5200, of which 49 per cent were polymorphonuclear, 16 per cent large mononuclear, and 34 per cent lymphocytes. The Wassermann reaction was still positive in spite of previous treatment.

After an eight weeks stay in the hospital the patient was much improved on rest in bed and antiluetic treatment, and was discharged with directions for x-ray therapy to the thyroid. The amount of x-ray given was not sufficient to expect any results.

On March 5, 1920 she was readmitted. When she left the hospital eleven months previously she weighed 115 pounds. When readmitted she weighed 129 pounds. During the first seven or eight months at home she felt better, but during the last three she was distinctly worse. Her neck had become larger, she had grown more nervous and irritable, and had not been able to sleep. Her feet had swelled and she became dyspneic on exertion. The tremor and sweating were more marked. Her physical examination was much the same as on the last admission, except that the struma had increased in size and the heart was more enlarged. Her basal metabolism was 49 per cent above normal. The white blood-cells numbered 2800, polynuclears, 40 per cent, lymphocytes, 52 per cent, large mononuclears, 7 per cent. On March 18th the basal metabolism was 47 per cent above normal and the glucose tolerance test was as follows:

	Blood-sugar	Glucose in urine
Fasting	0.91 per cent	
15 minutes after glucose ingestion	15 "	0
60 minutes after glucose ingestion	19 "	
120 minutes after glucose ingestion	16 "	+

The chemical study of the urine was carried out on a creatin-free diet. The patient received 2780 calories.

Date.	Nitrogen intake	Nitrogen output	Creatinin	Creatin	Uric acid
Mar 16	13.9 gm	12.77 gm	729 gm	387 gm	656
Mar 17	13.9 "	12.4 "	733 "	463 "	620
Apr 27	13.9 "	11.7 "	656 "	550 "	
Apr 28	13.9 "	11.0 "	636 "	428 "	
Apr 29	13.9 "	15.5 "	614 "	409 "	604

She was given medical treatment, rest in bed, high calorie diet, sedatives, and had all sources of infection removed. As

she did not improve, it was decided to operate. On May 12, 1920 a partial thyroidectomy was done, and except for a few stormy days following the operation, when she had a severe thyrotoxicosis, she made an uneventful recovery.

The postoperative examination of the urine revealed the following. The patient received a creatin-free diet containing 3400 calories

Date.	Nitrogen intake	Nitrogen output	Creatinin.	Creatin	Unc acid
June 14	15.3 gm	9.37 gm	725 gm	024 gm	570 gm
June 15	16.0 "	7.68 "	537 "	00 "	
June 16	16.4 "	9.89 "	523 "	00 "	739 "

Her basal metabolism on June 12, 1920 was 35 per cent above normal and she showed symptomatic improvement. On July 8th, just prior to discharge, her metabolic rate had come down to 28 per cent above normal. Since her discharge she has been seen frequently. She has gained in weight, is not nervous and is much improved, though her metabolic rate on two occasions has been around 40 per cent above normal. The most recent determination (January 10, 1921) showed a metabolic rate of 35 per cent above normal, she is beginning to get more nervous, her pulse is around 120, and she is distinctly in need of further treatment. As two previous postoperative cases showed a marked fall of metabolism on x-ray therapy, it is proposed to observe the effect of this treatment before resorting to further operative procedure.

Here we have three young adults with very obvious hyperthyroidism—with typical histories, symptoms, and signs. They were all very nearly of the same degree of toxicity, if the basal metabolism may be used as an index. On closer examination of the data, however, certain differences were apparent.

Case I was a young man who in spite of a severe thyrotoxicosis, with more than a 50 per cent increase in his metabolic rate, was not losing weight and whose carbohydrate metabolism was essentially normal when judged by the blood-sugar curve and the behavior of the respiratory quotient after glucose in-

gestion¹ The cardiovascular system, though, was badly hit—he had a very rapid, totally irregular pulse and the electrocardiogram showed auricular fibrillation He was one of the few cases studied that never excreted creatin on a creatin-free diet, even though he showed a minus balance of nitrogen during the period of observation Therapeutically, however, he gave brilliant results under the ray, with a fall in the basal metabolism, disappearance of all the symptoms of hyperthyroidism, gain in weight, and a return of the heart to a normal rhythm

Case II was also a young man with much the same findings, but with a regular and less rapid pulse On study, however, he revealed an apparently decreased ability to store glucose and glycosuria after glucose ingestion, *i. e.*, a so-called decreased sugar tolerance There was creatinuria on a creatin-free diet associated with a negative nitrogen balance Rest in bed on a high calorie diet improved him somewhat, but did not decrease his metabolism perceptibly Even three months' quiet sojourn in the country on a high diet failed to bring his metabolism down much, though his general condition and symptoms were somewhat benefited Under radiotherapy improvement was very rapid and the metabolism promptly fell, so that he returned to his very strenuous occupation against our advice

Case III was a patient who had been seen in the hospital previous to the onset of her present trouble There was a pretty distinct eleven months' history of hyperthyroidism, coming on rather abruptly under observation in the surgical follow-up clinic On the admission before the last she had had some radiotherapy, but the dosage was small and it was given irregularly and without benefit She appeared very toxic, though her basal metabolism was only 47 per cent above normal She showed a somewhat decreased ability to store glucose, though there was only slight glycosuria following its ingestion She excreted rather large amounts of creatin, though her nitrogen

¹ In some work on hyperthyroidism, which is to appear later, the respiratory quotient was followed physically after glucose ingestion The results obtained point to a decreased ability on the part of the tissues to store glucose rather than to an actual decrease in sugar tolerance

balance was positive throughout the greater part of the experiment. Rest in bed on a high diet and the removal of foci of infection did not benefit her. A partial thyroidectomy did improve her symptoms for a time and also caused a disappearance of the creatinuria and a slight fall in her basal metabolism. The latter, however, was not maintained for long. With a return of the symptoms the basal metabolism rose to about its initial level, where it has remained since. She has now been started on a course of radiotherapy.

Creatinuria in hyperthyroidism has been explained by assuming that the energy required for the increased metabolism is partly met by the decomposition of muscle tissue which leads to a liberation and excretion of creatin. While this theory appears logical and obvious, it does not explain the creatinuria in those cases of hyperthyroidism that are maintaining their weight and actually storing nitrogen. Here the increased rate of creatin liberation or production may be due to a stimulation of this particular mechanism by thyroxin or other substance elaborated by the diseased thyroid.

CONCLUSIONS

- 1 Basal metabolism is very helpful in controlling therapy and judging the toxicity of hyperthyroid patients.

- 2 From an analysis of the symptomatology, laboratory studies, and therapeutic results in these cases it appears that all cases of so-called Graves' disease are not fundamentally alike.

- 3 The occurrence of creatinuria in hyperthyroidism has not been satisfactorily explained in all cases. It does not seem to be related to the nitrogen balance.

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CONTRIBUTION BY DRS HERMAN O MOSENTHAL AND HENRY E MARKS

POST-GRADUATE HOSPITAL

THE CLINICAL VALUE OF BASAL METABOLISM

Fundamental Principles of Basal Metabolism The Determination of Basal Metabolism by Means of the Benedict Portable Respiration Apparatus Facts of Importance to Clinical Medicine that Have Been Obtained by the Study of Basal Metabolism in Obesity, Diabetes Mellitus, Cardiorenal Disease, Nephritis, Pernicious Anemia, Leukemia, Typhoid Fever, and Diseases of the Thyroid Gland

INTRODUCTION

THE extensive researches of Eugene F DuBois and Francis G Benedict and their collaborators have succeeded in making data concerning the rate of energy production of distinct clinical importance The recent development of various forms of apparatus that are so simple that they may be utilized as part of routine procedure in formulating diagnosis and guiding treatment has given considerable stimulus to the study of basal metabolism in disease

BASAL METABOLISM AND ITS DETERMINATION

The minimal heat production in the postabsorptive state, that is, fourteen or more hours after the taking of food, constitutes an individual's basal metabolism, the heat production is at its minimum while the subject is at complete mental and physical rest The heat production may be measured in one of two ways first, by the method known as direct calorimetry, second, by indirect calorimetry Direct calorimetry, as the name implies, measures the actual heat produced by the subject within a small chamber This procedure is much too complicated to be of use in the usual hospital, clinic, or office Indirect calor-

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metry determines the heat production by measuring the amount of oxygen consumed and the quantity of nitrogen and carbon dioxide eliminated. Accurate observations may be obtained from the quantity of oxygen utilized without paying attention to the carbon dioxide or nitrogen. By thus reducing the data required the basal metabolism determinations have been brought within the reach of many to whom the machines and procedures of a few years ago would have proved to be impracticable.

The criterion for heat production is the number of calories produced per square meter of body surface during a given unit of time. The surface area of each individual is different, but it is easily calculated according to DuBois' chart or formula if the height and weight are known. The normal basal metabolism also varies somewhat according to the individual's age, for which due allowance must be made. The average standards are furnished by DuBois, a variation of 10 or even 15 per cent from the average is to be considered within the normal limit.

NOTES ON THE DETERMINATION OF BASAL METABOLISM WITH THE "BENEDICT PORTABLE RESPIRATION APPARATUS"

No attempt will be made at this time to cover the technique of respiratory gas determinations with the various forms of apparatus now available. We have had some experience with the Benedict portable respiration apparatus, and a few observations concerning its use may be of value to you. This machine gives very accurate measurements of oxygen consumption by measuring the change in volume of the gas in a closed circuit, the CO_2 being absorbed by passing the air through a jar of soda-lime. A spirometer with an accurately balanced bell is included in the circuit, the counterweight bears an indicator, and the fall of the bell as oxygen is consumed is measured on a scale. Readings of the height of the spirometer bell are made at the beginning and end of a measured period, and check readings are also made over measured portions of the period, according to the Emmes method, these latter are termed "inside readings." From these readings of oxygen consumption and time the oxygen consumption per minute is calculated, this

volume is corrected to standard conditions (0° C and 760 mm pressure) from the readings of temperature and of barometric pressure which are taken, and then, using an assumed average of ± 825 calories per liter of oxygen (corresponding to a respiratory quotient of 0.82) the total calories per hour are calculated. The patient's body surface having been determined from the height and weight measurements, in accordance with Du-Bois linear formula or his height-weight chart, the calories per square meter per hour are found and compared with the standards of average values, based on age and sex.

The patient should be in the postabsorptive state, that is, at least fourteen hours should have elapsed since the taking of food and furthermore, he should be kept at rest for half an hour before the period of observation is begun. It is our custom to ask the patient to take no food after 7 P. M. on the day previous to the examination. He reports at the laboratory at 9 A. M. and is made comfortable in the recumbent position, with the clothing loosened if necessary, so as not to interfere with respiration, he is then instructed as to the nature of the test and the necessity of lying completely relaxed and at rest. After twenty to thirty minutes the mouth-piece and nose-clip are adjusted and about ten minutes are allowed for the patient to accustom himself to them. He is told that the accuracy of the test depends upon his breathing naturally and unconsciously, and that he should pay no attention to the apparatus, but should try to forget that he is breathing in any other than his accustomed way. When he appears to be breathing naturally and regularly the valve is turned and the stop-watch started.

In order to determine the shrinkage of the air in the circuit accurately the readings at the beginning and termination of each period are taken at the end of a normal expiration. Herein lies the largest source of error with this method. Occasionally a patient will be found whose respiration is so irregular that it is impossible to obtain results that check satisfactorily, usually, however, the expirations are fairly regular and the change in volume of the spirometer with each expiration represents the oxygen consumption. Each reading should be

checked by noting the descent of the indicator at the end of the previous or succeeding expirations, in this way one is enabled to judge whether the reading was taken at the end of a normal expiration and to apply a correction if it appears not to have been so taken. For example, in beginning the period the valve is turned and the stop-watch started at the end of what appears to be a normal expiration. The indicator is then closely observed over half a dozen successive regular expirations and the valve is turned and the stop-watch snapped at the end of the next. If the indicator is not caught at the exact point where, by deduction from the preceding expirations, it should have stopped, the error is kept in mind, and, after the air is completely washed and shrinkage has stopped, the reading of the scale is corrected by the amount of the error.

In making inside readings the same method is used, the expirations being watched both before and after the one which is taken as the start or end of the period, and the correct reading derived from these rather than from the actual reading itself. By holding the watch close to the scale the time reading can be made within a fraction of a second after the scale reading without the necessity of stopping the watch. The temperature is then read and noted. Readings of the scale are most easily made against the upper edge of the indicator and are estimated to tenths of a millimeter.

In patients whose respiration is quite irregular the degree of accuracy depends upon the degree of success in estimating the correct position of the indicator at the moment of starting or ending.

A second important source of error is low activity of the soda-lime. If too dry, the soda-lime will not absorb properly and should be moistened. If too wet, however, it may cake and interfere with proper ventilation. The use of a calcium chlorid jar in the circuit before the soda-lime container will prevent this, but as the dry air tends to take moisture from the soda-lime and thus decrease its activity, the calcium chlorid should be removed whenever the absorptive power of the soda-lime seems to be decreasing.

Activity of the soda-lime may be tested by tapping the outlet of the soda-lime jar and passing a sample of air taken from this point through a solution of barium hydroxid. A convenient index of its activity, however, is furnished by the length of time and the amount of shrinkage observed during the washing of the air after the period is ended. After the valve is closed the index should not rise more than 5 or 6 mm further, and it should come to rest in one minute or less. Prolonged shrinkage after the period is ended is an indication of exhausted or dry soda-lime, of insufficient ventilation, or of a leak in the apparatus.

The routine tests for ventilation rate and for leakage should, of course, be made each time the machine is to be used. There should be no change in the scale reading in ten minutes when a 100-gram weight is placed on top of the spirometer bell. If there is loss of gas, the following method is of assistance in locating the leak. The inlet tube is detached from the spirometer and closed with a tightly fitting rubber stopper. The spirometer bell is removed and the outlet is closed in the same way. A Y-tube is then used to connect a blood-pressure manometer and inflating bulb to the oxygen inlet of the machine. Air is now pumped in to a pressure of about 100 mm Hg, the faint hiss of the escaping air will often indicate the location of the leak and soapsuds will show its exact position.

It must be remembered that atmospheric conditions inside the machine during the period are different from those found at the beginning or end of the period. At the latter times the air is dry and free from CO_2 , while during the period both are present to a degree dependent upon their rate of production and absorption. This is a point of equilibrium which is reached only after the machine has been running an appreciable length of time. In order to avoid error from this source it is necessary that the air inside the machine should be at the same point of equilibrium as regards water vapor and CO_2 content at the beginning and end of the inside periods. The first inside reading is therefore not made until at least two minutes after the beginning of the period. It follows also that check-periods

cannot be computed which begin with an outside reading and end with an inside, or vice versa

As regards the question of correcting the barometer readings for water vapor tension, it may be said that at the time the outside readings are made the air in the circuit is very nearly dry. If the soda-lime is actively hygroscopic the water vapor tension at the time of the inside readings is also far from the saturation point, so that to make a correction from the usual tables which give the water vapor tension in saturated air at various temperatures would probably introduce fully as great an error as to make no correction at all. Benedict's experiments for the determination of water vapor tension at various points in the circuit gave very low figures, so that it would seem better *to make no correction for this factor, a comparison of inside and outside figures in our series of determinations appears to bear this out*

CO₂ determinations with the Sanborn Benedict apparatus have not, in our experience, proved satisfactory, the blower not being sufficiently powerful to maintain proper ventilation through the amount of absorbing substance that was necessary. When the calcium chlorid was reduced sufficiently in amount to permit proper ventilation it was found that a certain amount of water vapor was apparently carried through the first calcium chlorid jar and into the soda-lime jar, where it was measured as CO₂. Possibly with a more powerful blower or more active calcium chlorid than we were able to obtain satisfactory measurements might have been made, but the similar experiences of others lead us to believe that the use of sulphuric acid jars for absorbing water is necessary for reliable work in determining respiratory quotients, and that with this form of apparatus a more powerful blower is required

BASAL METABOLISM IN DISEASE

The following table, taken largely from the writings of DuBois and his collaborators, indicates the variation of basal metabolism that has been observed in the diseases and pathologic states thus far studied

TABLE I BASAL METABOLISM AS REPORTED IN VARIOUS DISEASES

	Percent basal metabolism above or below average normal		
Normal	-15	to	+15
Obesity	-14	to	+10
Diabetes mellitus			
Severe	-19	to	+23
After fasting	-36 (lowest observed)		
Emaciated	-37	to	-10
Cardiorenal without dyspnea	-10	to	+10
Cardiorenal with dyspnea	+25	to	+50
Nephritis with edema	-40	to	+14
Nephritis without edema	+2	to	+29
Pernicious anemia	+2	to	+33
Leukemia	+21	to	+123
Typhoid fever		As high as	+50
Tuberculosis (temperature about 104° F)	+15	to	+35
Tuberculosis (no fever)	-33	to	+15
Prolonged undernutrition	-30	to	-10
Exophthalmic goiter			
Very mild	+15	to	+30
Mild	+30	to	+50
Severe	+50	to	+75
Very severe		Over	+75
Cretinism and myxedema	-40	to	-15

These figures have been taken largely from the publications of E. F. DuBois and his collaborators, though other sources have been consulted

Obesity—There are some cases of obesity which are due to disturbances of the internal secretions. The types brought on by the diminished activity of the thyroid and hypophysis are familiar to all of you, and may be diagnosed in large part by their clinical characteristics. In doubtful cases, however, a determination of the basal metabolism will be of very great help. In the hypothyroid cases the basal metabolic rate is below normal. In the more common form of obesity, due to overeating, physical inactivity, and a placid disposition, the metabolism as measured by the surface area is within normal limits. Evidently the increased body bulk, due to the "inert fat," has not the same effect in reducing metabolism as the "inert fluid" has in edematous patients. The former are up and about and the latter are usually bedridden and undernourished,

these differences may be the determining factors in maintaining or lowering the basal metabolism. In treating obesity it is obvious, in view of the normal metabolic rate that exists in these individuals, that the addition of thyroid preparations to the subcaloric diet as an "accelerator" for the loss of weight, must be carefully watched. In these cases, symptoms of hyperthyroidism often follow even comparatively small doses, tachycardia, cardiac irregularities, headache, nervousness, restlessness, diarrhea are prone to develop and must be guarded against. In every case of obesity loss of weight does not ensue upon the use of thyroid medication, though the drug is given to the point of mild intoxication.

Diabetes Mellitus—An increase in basal metabolism is not found in most cases of diabetes mellitus. However, there may be acute phases in the course of the malady in which protein destruction and consequent nitrogen loss exceed the normal level. During such periods the basal metabolism is raised above the usual average. Allen and DuBois do not believe that acidosis plays a part in elevating the basal metabolic rate. Instances of the above phenomenon are rare, and when they do occur they must be treated by the usual measures, and there is no great advantage in having actual figures for the basal metabolism.

The more common finding in diabetes mellitus is that the basal metabolism is distinctly below the normal level. Undernutrition and lack of muscular activity are responsible for this phenomenon. Such patients can maintain their energy and heat balance on a lower food intake than normal individuals. One of the objects of starvation in treating diabetes is to bring about such a state of affairs. While it has the advantage of establishing maintenance at a lowered caloric level, it entails loss of mental and physical efficiency in some cases, while it increases the strength and sense of well being in others. These effects should be considered carefully in every instance and the treatment regulated accordingly.

Determinations of basal metabolism are not necessary for the successful handling of diabetes mellitus. The principles

just set forth may be taken for granted and utilized as established facts. Because of the diminished power of the body to break down glucose in diabetes the usual proportions of O_2 consumed and CO_2 excreted do not persist. Hence the basal metabolism in this disease cannot be determined by the simple machines that measure the O_2 made use of by the body, but requires a knowledge of the CO_2 eliminated as well.

Nephritis and Heart Disease—In cases of mild nephritis and compensated cardiac disease the basal metabolism ranges within normal limits. In some instances in cardiorenal patients the metabolism rises as high as 50 per cent above the average. Dyspnea is the factor that produces this change, the muscular effort entailed by the increased respiratory rate is presumably responsible. On the other hand, in some cases the basal metabolism is considerably lowered, in patients who have much edema it may be as much as 40 per cent less than the average. The edema increases the surface area by distention with an inert fluid, and it is perfectly plausible that a lower metabolism as measured by surface area should be present under such circumstances. A rise in blood-pressure, the presence of an acidosis or the existence of even marked impairment of renal function, as measured by the conventional tests, does not influence the plane at which metabolism proceeds. The abnormally high metabolism occurring in certain nephritics has been attributed to the dyspnea and restlessness characteristic of the severe types of the malady, previous fasting and undernutrition may be responsible for some of the low figures presented. Furthermore, a study of the respiratory quotients makes it evident that the metabolism of proteins, fats, and carbohydrates is in no wise disturbed in the cases of heart and kidney disease thus far observed in the calorimeter.

In isolated instances in very severe nephritis a determination of the nitrogen balance has shown that a toxic destruction of protein must exist at times at least. This apparently occurs most frequently when such patients are moribund and the phenomenon thus assumes a position of minor clinical importance.

From the physician's point of view some of these facts are of very great value. Dyspnea and edema in themselves demand immediate symptomatic treatment, and the determinations of basal metabolism are not of any aid in making either the diagnosis or therapy more precise. The knowledge that hypertension, acidosis, and renal insufficiency do not alter the metabolic rate or result in any change in the nephritic or cardiac patient that impairs their ability to utilize proteins, fats, or carbohydrates, gives the clinician a very sound foundation upon which to proceed when the very important dietetic side of treatment is determined on in this group of cases.

Pernicious Anemia — The increase of basal metabolism present in pernicious anemia may be somewhat unexpected. The languor of such patients certainly does not indicate it. The rapid regeneration of blood-cells, and the extra effort required from weakened and impaired muscles in carrying out the bodily functions, especially the respiration and circulation, with the increased frequency of the respiratory rate and heart-beat, may explain the rather marked rise in basal metabolism occurring in anemia. These observations indicate why rest and a high caloric régime are efficacious in bringing about an amelioration of the condition. The high diet is generally acknowledged as being desirable, but it is carried out conscientiously in but few cases. This is partly due to the fact that many of these patients have poor appetites, and, in part, it may be attributed to the lack of care in administering such diets. It is a common experience that "forced feeding," when it is actually analyzed, really provides a subcaloric ration. In those cases in which a high diet of 3000 to 5000 calories has been carried through the results have been remarkably good, the red blood-cells have increased and the general condition has been improved.

Leukemia — The very high basal metabolism characteristic of leukemia is extremely interesting. The rise is so great that the only theoretic explanation of this state of affairs does not seem to be entirely adequate, it is claimed that the process producing the great number of white blood-cells may be responsible for the increased metabolism, whether other factors also play

a rôle remains to be determined. It is perfectly evident from the facts thus far obtained that these cases must have a diet of a caloric value considerably in excess of the normal if they are not to become weak and anemic.

Typhoid Fever—The basal metabolism of typhoid fever is considerably increased. In some cases it rises higher than 50 per cent above the normal. The increase is roughly proportional to the height of the fever. These observations hold true for the febrile period. During convalescence the basal metabolism drops at first and then rises to 15 to 20 per cent above normal. It appears that there is an increased protein destruction in typhoid fever as shown by the large amount of nitrogen eliminated by such patients, this increases the basal metabolic rate. In addition there is an augmented heat production without a corresponding rise in heat elimination. This results in fever and an additional rise in metabolism. These abnormalities unless met by some therapeutic measures will emaciate the typhoid patient, jeopardize his chances of recovery, and prolong his convalescence. The efficacy of the high caloric diet of Shaffer and Coleman in meeting the situation is now a matter of history, everywhere that typhoid is treated food is administered according to the principles laid down by these observers. These patients absorb their food well, the high diet does not increase heat production. The nourishment given largely in the form of carbohydrates prevents the loss of the protein and fat from the body tissues and thus maintains the weight and strength as far as this is possible, by symptomatic treatment, 3000 calories a day appears to be the amount of food which meets the needs of most cases of typhoid fever, however many believe that this may be increased with good results, especially as the loss of nitrogen and destruction of body protein is thus more certainly prevented.

These very great advances in the treatment of typhoid fever have been based on metabolism studies involving the nitrogen balance and heat production. The large number of observations made give us a concrete idea as to the kind and quantity of food to be administered. It is impossible to make frequent

metabolism determinations on each patient, and it would probably be of no great value to have them since the course of the disease can be judged sufficiently well by the temperature curve. We should, however, always be willing to acknowledge our debt to those who have so painstakingly studied the metabolism of typhoid fever and given us an efficient means by which we can combat many of the most dreaded symptoms and complications of this disease.

Tuberculosis—The optimum amount of food for tubercular patients has been an open question for some time. Forced or moderately high feeding has usually been administered, varying amounts of protein have been given to these patients, the quantities have varied largely according to the "clinical impressions" of the physician in charge, on the one hand, and the resources of the hospital or patient on the other. McCann and Barr have recently investigated this problem by means of metabolic studies and have put it upon a rational and much more definite basis.

The basal energy requirement of the tuberculous individual is given in Table I. It is apparent from these figures that the patient with no fever or only a slight rise in temperature has a basal metabolism that does not exceed the extreme normal limits. When the body temperature rises considerably, to about 104° F, the metabolic rate goes up materially. Coughing and restlessness as well as the fever are responsible for this increase. When the coughing and restlessness are eliminated it appears that the basal metabolism characteristic of a temperature of 104° F is but plus 29 per cent of the average normal standard instead of plus 40 per cent. In nearly every instance the basal metabolism, during the afebrile stage, is lower than for the same individual calculated for his normal weight. All these facts indicate that the heat production and metabolic rate in tuberculous cases are not, contrary to a wide-spread belief, very materially increased.

There is no change from the normal in the respiratory quotients, thus indicating that proteins, fats, and carbohydrates are utilized in normal fashion. Furthermore, the destruction

of protein in this disease, while greater than normal, is not nearly as marked as in typhoid fever

The conclusions in regard to the diet appropriate for the tuberculous subject may be expressed most concisely if quoted from the paper of McCann and Barr "During periods of activity of a pulmonary tuberculosis the diet need not contain more than 500 calories above the basal requirement (from 2000 to 2500 calories), nor more than 60 gm of proteim The object of such a diet is to maintain the respiratory activity at the lowest level compatible with the maintenance of nitrogen equilibrium To achieve this purpose it is just as necessary not to overfeed as it is to maintain muscular rest

"When the activity of the disease has subsided the total calories in the diet should be raised to meet the requirements of the patient as his muscular activity increases The protein intake could also be increased to enlarge the repair quota "

It appears that overfeeding the tuberculous patient has detriments which heretofore have not been generally recognized As a result of metabolic studies a rational diet which meets the needs of the situation exactly has been outlined

Diseases of the Thyroid Gland—The first intimation that the metabolism in exophthalmic goiter was abnormal was given by Friedrich Muller in 1893 He found an increased nitrogen output and thus demonstrated an excessive protein destruction in this disease This comparatively simple observation has been the starting-point for the many experiments and studies that have served to illuminate the problems of hyper- and hypothyroid symptoms Upon them the rational principles of treatment have been based Very recently the methods of estimating the metabolic rate have been simplified a great deal, and it is possible to make rapid and frequent observations of the basal metabolism These determinations provide what is acknowledged to be the best means of making a diagnosis of over- or underactivity of the thyroid gland, and, furthermore, they furnish criteria which guide the surgical, Roentgen ray, and medical treatment

From Table I it may be noted that tuberculosis, cardiac

disease, undernutrition, obesity, and certain nervous affections may lead to the suspicion that the thyroid gland is functioning too actively or too little. In the event of necessity of differential diagnosis under these circumstances the determination of the basal metabolism is of very great help, inasmuch as all of the conditions mentioned vary much less from the average normal basal metabolism than do abnormal thyroid states. Other maladies, such as leukemia, cardiorenal disease with marked dyspnea or typhoid fever, whose basal metabolism approaches the intensity of that reached in exophthalmic goiter, may be diagnosed by physical examination and the usual routine laboratory tests without having recourse to the determination of their metabolic rate.

One of the best examples of the diagnostic value of the determination of the basal metabolic rate in medicine is that furnished by Peabody, Wearn, and Tompkins. Of 57 soldiers submitted to them for treatment, principally because of rapid heart action, nervous instability, and physical inferiority, 24 were diagnosed as cases of hyperthyroidism. The normal metabolic rate exhibited by these individuals disproved the diagnosis. This investigation shows conclusively that "nervous" patients do not necessarily have a high basal metabolism. Nervousness, tremor, slight enlargement of the thyroid gland, lagging of the eyelids and tachycardia were present in many of these cases, these signs and symptoms may therefore be considered of minor importance in making the diagnosis of Graves' disease. Bruits and thrills over the thyroid gland, a tachycardia which persists when the patient is at rest, and loss of weight appear to be of greater significance.

The data obtained in individual cases may possibly serve to illustrate the usefulness of the basal metabolic rate as a diagnostic measure better than generalities.

The following is the synopsis of a case referred as one in which it was indicated to determine the intensity of the hyperthyroidism. This was a woman of forty years, a housekeeper, she has been exceedingly nervous and irritable, her sleep has been considerably disturbed, she has complained of sweating,

chilly sensations and hot flushes both during the day as well as the night, she has no reserve strength and becomes very easily tired, there has been a loss of weight of 28 pounds in three years, some dyspnea has been present when the patient was quiet, this has been considerably aggravated on exertion, she has complained of cardiac palpitation, vomiting or diarrhea have not been manifest at any time. Physical examination showed the patient to be rather thin (weight 110 pounds with clothes, height 5 feet, 3 inches) and very nervous, there was a distinct tremor, a pulse rate of 120, which dropped to 84 on resting, the skin about the face and neck was hyperemic, but otherwise normal, there was no exophthalmos, Moebius' or von Graefe's sign and examination of the thyroid gland revealed no abnormalities.

After various forms of therapy, which did not prove to be of value, her physicians were considering the advisability of more active interference with the functions of the thyroid gland, the possible diagnosis of Graves' disease certainly seemed justified. Her basal metabolism proved to be 94.3 per cent of the normal standard and therefore well within normal limits. Hence this patient's symptoms are not due to hyperthyroidism and attempts to curtail the activity of the gland, while they might serve to ameliorate some of the complaints, would be likely to play havoc in other directions.

A case which illustrates the difficulty of diagnosing Graves' disease from the history and physical examination alone is the following. A tailor, a Russian Jew, complains of epigastric distress for two years and pains in the right lumbar region for one year, all the large joints ache at times, there are frequent and severe headaches, he is very constipated and has never had diarrhea. The thyroid gland is slightly enlarged, but gives no evidences of bruits or thrills, there is a very slight prominence of the eyeballs, but all the other eye signs are negative, a fine tremor of the fingers is present, the pulse-rate at different times varied between 84 and 120, the hands were cold and blue. The history and physical examination gave the impression that this was a case of nervous instability resembling the instances of

neurocardiac asthenia that gave rise to so much discussion during the war. His basal metabolic rate, however, was 41 per cent above the normal value. This figure is too high to be accounted for by possible restlessness during the determination or by the slight tachycardia. The inevitable conclusion is that there is a distinct overactivity of the thyroid in this man.

The nervousness, tremor, and suggestive exophthalmos were virtually the only ones of the accepted signs of hyperthyroidism that were present. Why the tachycardia was not constant, why the eye signs were not more definite, why there was no diarrhea, are questions that can be answered in many different ways. However, it brings up the very important clinical fact that many of these cases apparently present a dissociated group of symptoms that render it very difficult at times to make an accurate diagnosis or to obtain ideal therapeutic results. Thus we have had one patient who complained of cardiac palpitation after the use of thyroxin and thyroid extract, although her basal metabolism was still 14 per cent below normal. In another instance there was marked excitability and nervousness, though other signs indicated hypothyroidism, and the metabolic rate was 23.2 per cent below the normal figure, in this case the administration of thyroid gland had a distinct tendency to produce diarrhea and increase the nervousness without materially affecting the pulse-rate, the weight, or the feeling of lassitude. In this patient there had been a complete hysterectomy some years before. The question of the depression of the basal metabolism, through loss of the ovarian function, is suggested by these findings. Janney and Henderson described 2 similar cases in which the ovaries had been removed. In these the basal metabolism could not be brought to normal, as symptoms of distress, palpitation, and rapid pulse intervened even on small thyroid doses.

In occasional instances the basal metabolism apparently does not serve as an exact indication of the activity of the thyroid gland. Janney and Henderson report a case with thyroid hypertrophy, tremor of the fingers and tongue, sympathicotonia, moist palms and soles, nervousness, excitability, exophthalmos

Stellwag's sign, rapid pulse on slight provocation, and loss of weight and strength, while the basal metabolism was 5 per cent below normal. These authors believe this to be a case of exophthalmic goiter in spite of the normal metabolic rate. In one of our patients, a very obese lethargic woman, the basal metabolism proved to be normal. She was given thyroid cautiously and the dose gradually increased to the rather large dose of 15 grams a day which has been maintained for more than six months. During this period the lethargy has diminished very markedly, there has been some loss of weight, the pulse-rate only goes up to 80 after exercise, the temperature still continues to be subnormal. The only signs of too high a dosage of thyroid substance are excessive perspiration and a headache, which comes on every one or two weeks. Both of the above cases are possible examples of disagreement between what appear to be justifiable clinical diagnoses and the basal metabolic rate. Such occurrences are exceptions, and it is a matter of further study and observation to clear up the exact relationship of such findings.

Clinical signs and symptoms have been sought which would parallel basal metabolism determinations and thus make such estimations of secondary importance. The two criteria most often used are the pulse-rate and the weight. Neither of these appear to meet the demands as a measure of the intensity of thyroid activity as satisfactorily as the estimation of the metabolic rate. The conclusions of some of the observers who have worked extensively on these problems are of interest. Sturgis and Tompkins conclude that there is a fairly constant relationship between the resting pulse and basal metabolism, a tachycardia of 90 or higher was associated with a basal metabolism of 15 per cent or more above the normal in all but 16 per cent of 154 patients with hyperthyroidism. When the basal metabolism came to normal the pulse came to below 90 in 78 per cent of the cases, the pulse-rate gave an accurate idea of the course of the disease compared to basal metabolism in 85 per cent, the fact that a pulse-rate at complete rest below 90 is seldom and below 80 per minute is rarely associated with an

increased metabolism, is of practical importance in the recognition of a group of nervous patients whose symptoms resemble those occurring in hyperthyroidism

Means and Aub make conclusions that vary somewhat with those of Sturgis and Tompkins. They find that the pulse-rate is not an index of the absolute degree of thyroid intoxication, but that the pulse-rate does furnish a relative index in the same case seen at different times, that is, as the basal metabolism rises or falls, the pulse-rate in the same person increases or diminishes proportionately, but a given pulse-rate is not an indication of a corresponding basal metabolic rate in different individuals, in making comparisons between the pulse-rate and the basal metabolism they use a standard by which pulse-rates of 50 and 150 are equivalent respectively to a normal metabolic rate and to a rate 100 per cent above normal, on this basis there are two types of hyperthyroidism, Type 1, in which the pulse-rate is 10 or more above the metabolic rate, and Type 2, in which it is 10 or more below, Type 1, that with the more marked tachycardia, does equally well on being treated with γ -ray or surgery, while Type 2 apparently gives poor results with immediate resort to surgery, but does better with preliminary use of γ -rays

From the conclusions and the experience with tachycardia which any clinician has at his disposal, it is safe to say that from a diagnostic point of view the pulse-rate is not as reliable a diagnostic sign as the metabolic rate

The only other symptom which has been proposed as a measure of the intensity of thyroid activity or progress of thyroid disease is the loss or gain in weight, and here the comparisons with the metabolic rate are very far from being absolute criteria of one another. Thus Means and Aub find a reciprocal relationship between the weight and basal metabolism in only 20 per cent of their cases

The basal metabolism furnishes the best measure by which to gage the effect of medication, γ -ray, or operation. Most of the published results indicate that this is a simple matter. A closer study of many of the tables, however, shows that the final "cure" can only be accomplished after months of effort

The metabolic rate is the only test that gives a satisfactory answer to the difficult question whether the activity of the thyroid needs further curtailment or whether thyroid medication should be increased. The following instance may possibly accentuate this point. In April 1919, a young woman of twenty-eight had the right lobe, isthmus, and part of the left lobe of her thyroid gland removed, before the operation her basal metabolism was 34 per cent above normal, after the operation it dropped to 24 per cent above normal, one year and seven months after the operation the metabolic rate has almost returned to the preoperative level, being 32 per cent higher than the average normal. Hence in this case the nervousness, tachycardia, etc., which persist in spite of the operation are not due to nervousness, as it is tempting to assume, but to overactivity of the remnant of the thyroid gland.

The value of basal metabolism in diseases of the thyroid gland may be compared to that of hemoglobin in the anemias. In many cases no hemoglobinometer is necessary to determine the grade of anemia existing, in some instances, on the other hand, inspection of the skin and mucous membranes is very deceptive. The proper laboratory test gives us, in both conditions, a correct orientation as to the intensity and nature of the process. It is obvious that in a disease whose treatment involves the permanent interference with vital functions, by surgery or x-ray, such a test, as basal metabolism, furnishes an indispensable factor in judging whether the activity of the thyroid gland is normal, increased or diminished, in forming an accurate estimate of the intensity of the disturbance and finally in guiding the administration of thyroid preparations, the use of sedatives, rest, x-ray, or surgery. The fact that many cases may be diagnosed without the aid of this test of precision is no reason to neglect it as some clinicians seem to be desirous of doing. It is a great satisfaction to have a means at hand by which at least one disease in the field of endocrinology may be robbed of its mysticism and exaggerated prevalence, and be properly diagnosed and treated.

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CLINIC OF DR HARLOW BROOKS

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MANAGEMENT OF CONVALESCENCE IN LOBAR PNEUMONIA

AFTER the temperature has become normal in lobar pneumonia either by crisis or by lysis, in most instances the physician and perhaps the family also are likely to feel that the patient demands but little more from the attending physician. The subsequent management is too often relegated largely to the family in private practice or to the house staff and nurses in the hospital. Most of us largely lose our interest in the case. We may, in parting, as it were, say, that a trip to the South, a summer in the country, a slow return to business habits and ordinary life is desirable, but how many among us really take seriously to heart our further obligations to our patient?

I freely confess that this has been in the past very largely my attitude toward the convalescent in lobar pneumonia, and it was only my experience with pneumonia convalescents during the late war that my attention was sharply attracted to my obligations to the patient recovering from this disease. During the war I think that most of us felt an increased moral responsibility for the welfare and early restoration to a phase of normal efficiency of our convalescent cases, which was a new and surprising experience to a very considerable degree.

Experience showed us beyond question that few, very few men were fit to return to full duty in less than six weeks after the afebrile period of the disease had been reached, when the patient was able to sit up, get out of bed, and to perhaps walk about the ward. Some men were able to return to duty in this period of time, notably was this the case with members of the Medical Detachment, but I very soon became thoroughly im-

pressed with the fact that though a certain degree of physical fitness might be restored in six weeks, in but very few instances was the soldier able to return to full line duty. I think that I am quite safe in the statement that most men who had successfully recovered from uncomplicated lobar pneumonia were unable to take on full duty in less than three months after they had ceased to be bed patients. Very many healthy soldiers who had survived uncomplicated lobar pneumonia were unable to take over full duty in less than a year, and there are many who were never able to return to the full physical responsibilities of life. A review of the compensation lists of returned soldiers will beyond doubt show that many men have never returned to such a state of physical fitness as to be able to fully carry on under the requirements of normal life.

A conscience-smitten review of my cases in civil life since my attention has been called to this fact has led very naturally to the conclusion that this is equally true of cases in civil life, and perhaps even a greater degree of disability exists here because the soldier at least starts in with his pneumonia, as a rule, in good physical status, while many civil patients who contract and survive the infection have developed it when considerably below par, in one respect or another.

I feel that I and probably many others also have not fully in the past comprehended our responsibilities in this direction. My purpose in this talk is to point out in a way what may and should be done, in order that the after-effects of pneumonia may be mitigated and an earlier and more complete return if possible to full capabilities be insured. To begin with the beginning. As a general rule I believe that we are accustomed to allow our convalescent patients to get out of bed too soon. They should certainly never be allowed out of bed until the temperature has returned and remained at normal for at least a period of two weeks and until the definite signs of consolidation have chiefly disappeared from the lungs. We must remember that even in the most favorable cases of pneumonia, the heart muscle, the renal and hepatic parenchyma are more or less degenerated and that prompt recovery from changes of this character are im-

possible without *time* Where serious crippling has taken place, as particularly in instances of the more serious toxic cases, a much longer time is necessary if heart strain is to be prevented Far too many patients date their myocardial incompetence to a too early return to normal life strain after pneumonia

There is little doubt but that the albuminuria and the defective excretory possibilities of the kidney in pneumonia are in most cases but a reaction on the part of the kidney to the circulatory and toxic disturbances of the disease, and that under natural or ordinary conditions these quickly subside after the exudate has largely resorbed, but if normal excretory requirements are too early thrown on the kidney, already overburdened and already crippled by the circulatory and toxic conditions incident to the infection, a true nephritis will develop, as V Kahlden showed many years ago In such a manner does the chronic nephritis develop which probably has its inception in an incompletely convalesced pneumonia more frequently than we think off-hand to be the case

Normal or shall we say more advisedly, *usual* resolution does not always take place in the lung after a pneumonia Many conditions may conspire to this end, a defective circulation the presence of unusually wide thromboses of the pulmonary venules and arterioles, plugged and infected bronchi favoring the development of pulmonary abscesses, spots of delayed resolution, and doubtless still other lesions, such as interlobar empyemas, perhaps of very small extent originally All these favor a delay in resolution and we should always remain in a most suspicious frame of mind when the pulmonary exudate fails to clear promptly and universally, even though the temperature may remain at normal

Still another reason for great caution and circumspection in our decision to permit our convalescing cases of pneumonia to sit up and get out of bed is found in those cases in which a pleural effusion especially an encapsulated one persists, even though diagnostic tap may show the fluid to be sterile My experience has shown me that in such cases it is wise to aspirate the fluid if need be for there can be no question whatever but that en-

capsulated empyema frequently follows such conditions if they are allowed to remain and at the same time our patient is allowed to get up and about. It has also appeared to me that when there has been a large fibrinous pleural exudate, if we permit too early activity, either an empyema may develop or the resulting pleural adhesions become wide-spread and intimate so that serious after-crippling of the lung may follow.

There is still another condition, less definite to judge but equally important with those which we have thus far mentioned, which should prevent our permitting too early a release from bed and from careful clinical supervision. I refer to those cases in which a profound nervous and mental exhaustion or aberration is present. As a rule, of course, this is most frequent in cases which have shown a high grade of toxemia and prostration in the course of the active infection, but it also occurs in some unexplained instances in which the patient has not apparently been particularly sick during the height of the pulmonary consolidation, and in some in which the amount of the involved lung tissue has not been great. One, of course, sees such patients particularly frequently in the course of influenzal epidemics.

Long-standing and even permanent mental and nervous impairment follows such instances with sufficient frequency to at least indicate its importance, and the necessity that, particularly all cases in which an asthenic condition follows the disease, most careful attention should be paid to the patient and too early or too great additional nervous or emotional burden should not be permitted. Many of the cases seem to do best when kept in bed and under practically the régime of a rest cure until the mental excitement or nervous torpor are clearly passing away.

Finally, there is that class of cases in which a previous tubercular infection of the lung is known to have or is surmised to have pre-existed. In these cases in particular a more prolonged stay in bed is to be insisted upon and a frequent examination of the sputum and a carefully kept temperature chart must be carried out until this danger seems definitely to have passed.

In my opinion, it is in cases of this kind in particular that we find tuberculosis following pneumonia. I am of the opinion, though it is quite impossible to prove, that tuberculosis as a new infection rarely follows pneumonia, which does, however, frequently activate and disseminate an old infection.

Not only are all these factors to be taken into consideration in determining when we may most wisely, not alone most safely, allow our cases convalescent from pneumonia to get out of bed, but we must not forget the dangers of a reinfection with perhaps some other pneumonia-producing organism than that responsible for the original infection. Three instances of this kind occurred in my wards at Camp Upton, each time with another organism than the original one as the cause of the secondary pneumonia, but a recent author in a late number of the American Journal of Medical Sciences reports a small group of pneumococcus Type I cases in which a secondary infection or reinfection developed. I am certain, however, that this is not a frequent occurrence, but my extensive experience in conducting pneumonia wards during the war has convinced me that in many instances one attack of pneumonia sensitizes to secondary pulmonary infections, and I am completely convinced of the wisdom of the cubical system of case isolation, the wearing of masks by attendants and ambulant convalescents, especially in wards of convalescent pneumonia patients.

The conclusions to be drawn from this whole matter is that we must not allow our convalescent pneumonia cases out of bed too soon, that we must not at least encourage the mixing of infections, and that we must most carefully judge in each individual instance as to the proper time to allow them out of bed. I am quite certain that we should never let them out in less than two weeks after the temperature has returned to and remained at normal.

Perhaps it will be well if I elaborate briefly some of the points on which I base this judgment, though to a considerable extent I have already done this, but I believe further that we should most carefully supervise the first getting out of bed in all instances, allowing it to take place only in our presence or in

that of a competent and observant nurse or attendant. It is my custom to precede the getting up by having the patient sit up in bed for several days, having an attendant meantime carefully observe the patient's pulse and respiration as well as his general attitude when this is permitted. When this is accomplished without undue acceleration of the pulse and without the production of dyspnea or faintness, we are then ready to consider the advisability of allowing the patient to slip into or to be lifted into a chair by the side of the bed.

I presume that most clinicians have shared my experience of having patients in apparently good condition go into collapse at such a time, some to suffer from acute dilatation of the heart and die.

Nor can we consider our responsibilities and obligations to the patient discharged when they are able to sit up without undue discomfort, nor even when they are able to walk comfortably about the ward or corridors.

Our war experience emphasized most emphatically that a return to normal exercise must be very gradually accomplished, necessarily in some instances and advisedly in most. Most excellent results and much information as to the muscular weakness, particularly as regards the myocardium and the muscles of the extremities, was given us when we organized detachments of our convalescent pneumonia patients, giving them at first very mild exercises, breathing exercises, very much mitigated setting-up drill, short marches along the hospital corridors, and, as they gained in strength, out of doors, and finally real marches or hikes, either in close formation or at route step, as the character of the cases and their reaction determined.

All these exercises were done under the command of an officer or of a trained and discrete corps man who had the authority to excuse any man from the drill at any time and to promote to other classes or to demote to squads less advanced if any case showed undue fatigue or exhaustion, either mental or physical. Particular attention was given to breathing exercises, and it was found that our boys carried out these exercises much more satisfactorily and happily when in de-

tachments than when alone. As soon as possible the men were required to assume the position and attitude of a soldier, and all the exercises, even the mildest, were carried out in a strictly military manner and at command. It is surprising how much more interestedly men enter into such exercises when these conditions are insisted upon, and, as Henry Frauenthal long ago asserted, when the movements of body and mind are co-ordinated through example and imitation, and when under definite command. Almost without exception the men mentioned the greater pleasure and benefit which they derived under such control.

After sufficient progress had been made the men were given their arms and the manual of arms was gone through at first at a slower cadence and finally at one considerably faster than the normal. The men were then formed in squads and marched out and drilled in military formation, then given short preparatory hikes.

Gradually various articles of the equipment were added until the men were finally able to march for reasonable distances in the military cadence with full equipment.

The effect on the morale as well as on the physical stamina of the men was remarkable, and we finally did not permit discharge from the hospital until the men were able to carry on with these exercises without any undue fatigue and with but pleasurable exhilaration. I have never known such a man to be returned to the hospital after discharge, though previous to our adoption of these measures many had soon been returned, though in every instance including our full "graduates," the men were returned to their barracks marked "light duty" only.

Of course, under civil conditions such ideal conditions are rarely attainable, but the turning of our convalescents over to skilled and sensible athletic trainers or to gymnasia is quite possible.

Particular attention should be given to a military carriage as soon as this can be maintained without undue fatigue, for in this position proper respiration is best favored and great attention was paid to the breathing exercises of the setting-up

drill It is most interesting to observe under these measures the rapid clearing of physical signs and especially when it was practical to use frequent fluoroscopic examination

It goes without saying that no individual should ever be pushed beyond his capabilities nor should too rapid progress be attempted in any case The work should be carried on under the immediate supervision of a well-tempered attendant familiar with men and drill or under the immediate observation of a physician familiar with athletic work Among all these cases not one failed to benefit except those who suffered from some complication of the disease which commonly became soon evident under this training We believe that pleural adhesions in particular are limited under such a training and that the chest deformities or habits of malrespiration which so commonly follow pneumonia are greatly lessened, and a well-formed normally functioning thorax was given in cases, some at least of which might have suffered, as so many do, from malformations of the thorax where poor respiration and malposition and carriage follow incompletely convalesced pneumonia

As a rule, it is not necessary to resort to medication in convalescent cases of uncomplicated pneumonia, but considerable attention must be given to the diet, for example, where albuminuria persists it seems unwise to permit what is very frequently otherwise very desirable, that is, a diet rich in the animal albumins Iron is, however, very frequently beneficial and occasionally arsenic as well where the blood building appears to be tardy Digitalis may occasionally be necessary, but, as a rule, it is unwisely given in my opinion, for such cases as manifest deficient cardiac reserve are usually more in need of rest and carefully graduated exercise than of artificial and deceiving stimulation by drug methods

In all convalescent cases outdoor air, sunlight and rest, including plenty of sleep are, of course, to be fully utilized These measures, if it is possible to carry them out in a fairly satisfactory way, certainly must go far toward the prevention of a tubercular reinfection developing, and for the same reason the condition of the heart and kidney in particular permitting

a full and variegated diet is preferable. No attempt should, however, be made to "fatten" convalescent cases of pneumonia; the desideratum is increase of muscle tone and of respiratory function.

Modification of these methods are, of course, necessary in almost all cases where complications have developed in the course of the pneumonia. This is particularly true of cases which have extensive pleural adhesions or effusions and especially in convalescent cases which have suffered an empyema. We have utilized, and doubtless most have, the blowing bottles in such cases, but though they are undoubtedly useful, they are not nearly so definitely so in my opinion as carefully supervised breathing exercises when attention is also paid to the correction of developing thoracic deformities. We have already mentioned the desirability of removing pleural exudates in convalescent cases even when they are not infected, but this need not be done too soon, nor do I any longer urge the surgical drainage of mild empyemas in every case early especially when the infecting organism is not a pneumococcus.

Where pulmonary embolism has taken place with a resulting atelectasis of some portion of the lung, great care must be exercised, particularly in the institution of breathing exercises and physical drill; time must be allowed and a very slow return to relatively normal activities must be expected. A much more serious problem confronts us in dealing with cases in which pulmonary gangrene has taken place. Long confinement in bed is then essential and passive movements, massage, and other forms of bed exercise must be given to build up and maintain muscle tone and body resistance—the outcome is, of course, usually a very melancholy one.

This is also my usual experience with pulmonary abscess, particularly those which do not early open up into a bronchus and thus establish drainage. Where the abscess is interlobar, of course surgical intervention is to be sought as early as reasonably certain diagnosis can be arrived at, but I do not feel that this is by any means the case with instances of intralobar abscess. I have come to the conclusion that these cases are likely to do

better with palliative and time-consuming measures until the abscess may present through a pleural surface, in which case it is usually preceded by pleural adhesions through which the surgeon may more safely enter. The whole question of the treatment of convalescence must in these cases revolve about the question of the location of the abscess, that is a question which is too complex for such an occasion as this.

Pleuropericarditis is present in a very high percentage of pneumonia cases. In most, unless it is accompanied by an empyema, it requires no special convalescent treatment, but a very different matter confronts us when a pericarditis is present, and especially when the pericardial adhesions are intimate or if a pericardial empyema develops. In neither case do we dare to institute except very tentatively the physical exercises on which I have laid so much stress, and in most of these cases, sooner or later, the problem becomes a cardiac one and is usually best combated by rest rather than by exercise.

I have always felt that pericardial empyema is a surgical condition. I have never tapped the pericardium, as it were, blindly, except with great trepidation, and in most instances, if the exudate is sterile, or even if it be not highly purulent, I believe that it is wiser to trust to nature throughout the convalescence, limiting greatly physical activities and relying on purgation, reduction of salt and fluid intake, etc., rather than on tapping.

Where true pus is present in the pericardial sac I have seen no demonstrated clinical cases recover except from real surgical drainage, and I think that this should be resorted to sooner than is our usual medical custom, that is, I think that it should follow microscopic and bacterial confirmation of the clinical diagnosis. I have, however, seen several cases at postmortem where the appearance indicated that a purulent pericarditis had been cured spontaneously by nature, death following from some other cause. I believe that where the process is a tubercular one operation should be delayed to the last possible moment however.

We must be very careful not to introduce physical exercises

in cases of endocarditis occurring in the convalescence of pneumonia. Rest is the ideal condition here, and we must not be too pessimistic in these cases. I have seen several in which confirmatory blood-cultures were present which recovered under time. I do not believe that vaccine treatment is of any particular use in these instances though it may perhaps serve to maintain the patient's and physician's interest and optimism.

We must also largely interdict general physical exercise in cases of convalescent arthritis, and especially in cases of phlebitis, here again rest and time are our best and most helpful measures. Where metastatic abscesses or even synovial empyema develop I feel that, again, early resort to surgery is the safer and more conservative means. We must not in such complications rely too much or too long on nature and body resistance.

Meningitis is present in the convalescent stages of pneumonia in a very considerable number of cases, as a rule it develops in those cases which show also a generalized septicemia. In the way of treatment little is to be accomplished in the average case which in my experience goes on to rather early fatal termination. There can be no question, however, but that great symptomatic benefit is given these cases and the progress of the disease is delayed by lumbar tap and in case the infecting organism is a Group I pneumococcus, the specific serum may be introduced. I have never seen benefit follow from the introduction of the polyvalent pneumococcus serum nor have I personally seen any case of Type I meningitis, so I am unable to say if benefit will follow the introduction of this specific serum, but it is an experiment well worth trying. No benefit has followed the use of the vaccines in our hands either in pneumococcus or in streptococcus meningitis. One should, of course, always culture out the infecting agents in the cerebrospinal fluid because it is quite possible that organisms other than that responsible for the pneumonia may be present, thus in two cases in my recollection the meningococcus was found in cases of meningitis complicating convalescing bronchopneumonia, and the serum treatment gave us a good result.

In this respect also one must remember that the meningococcus may be the cause of the pneumonia, also several such instances have occurred in my experience, and certainly in these cases the intravenous and intraspinal use of the specific serum is certainly indicated

One of the most interesting and difficult convalescent conditions encountered in the management of late cases of pneumonia is the postpneumonic delirium or insanity. This condition is by no means infrequent, but the manner of its causation is absolutely unknown. It may be a natural result of the effects of the toxins on the ganglion cells, it may be the result of a pre-existing alcoholism, of a defective or crippled renal action, that is, a uremic condition, or it may be due to an actual cerebritis. In certain cases it has been suggested that the delirium is the effect of perhaps overdosage of digitalis. It is quite certain that its causation differs very much in different cases, and I believe that I have seen instances illustrating all of the theories mentioned except that of digitalis origin. I have never seen a case in which I felt that digitalis could be responsible, though I do believe that I have seen cases in which a defective circulation very probably was the cause of the delirium, for it disappeared when the condition of the circulation more nearly equaled the normal.

In the treatment of these conditions, in my opinion, the most definite benefit had been reached when rest was made the dominant key of the management, rest and time, particularly the latter. The surroundings of the patient must be made as conducive as possible to this end, sleep must be encouraged, if need be, by the administration of hypnotics, of which the morphin group should be last thought of for obvious reasons. Full attention must be paid to a normal excretion both by the bowel and by the urine and sweat, as a rule a full diet seems to be more desirable, and as soon as the physical condition of the patient permits, outdoor air, driving, and walking is to be encouraged up to the physical abilities of the patient. A long mental and nervous rest is necessary before full recovery of the patient can be expected.

Great mental exhaustion and depression is even more frequent than actual delirium, and I feel that this is a condition which we in the main, very much neglect. A good many cases recover, but very slowly, from the asthenia which follows healed pneumonia and in by no means a small number of cases the mental activities of the patient are seriously and permanently compromised. The effect is seen most strikingly in such patients as writers, painters, and others, such as musicians, whose work is largely creative in character.

In cases manifesting these symptoms rest and change, perhaps travel, is very beneficial. Camping trips and other diversions which distract the mental activities far from their accustomed paths in particular are beneficial, and a very considerable period of time must elapse before the convalescent is allowed to return to full mental activity and stress.

In this talk I have gone over the subject very rapidly, some of its most important phases have been little more than mentioned. It has been my purpose especially to attract your attention to the fact that our responsibilities toward our pneumonia patient are not discharged when the temperature has returned to normal, nor even when he is able to be up and about and when he is in a physical way apparently largely capable of caring for himself. If we are to send our patient back to his work and normal life requirements in the best possible manner we must do more than this, and our responsibilities and liabilities only cease when we have returned our patient to his usual life requirements in as normal and efficient a condition as it is possible to gain. The degree to which this approaches the normal depends very largely on the attitude of interest with which we study and care for our cases during the period of convalescence.

CLINIC OF DR. A. S. BLUMGARTEN

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THE RÔLE OF THE ENDOCRINES IN COMMON MEDICAL DISEASES

1 The Rôle of the Thyroid and Adrenal Apparatus in Gastric Neuroses.

2 The Relation of the Pituitary in Adolescent "Epilepsy" and Nocturnal Enuresis

THE rôle of the endocrine system in medicine has been coming more and more to the front in the last few years. The causes for this growing interest are not because the well-known endocrine syndromes are increasing in frequency, nor because physicians are learning to recognize these syndromes more readily, but because the thinking physician in his daily contact with disease encounters a stone wall in the attempt to explain many of the phenomena of disease on an organic pathologic basis. He soon begins to appreciate that patients suffering with the same disease or the same symptoms in different diseases have a great many anatomic physiologic and even psychic characteristics in common.

The variations in the reaction of individuals to various toxins are well known to any good clinical observer as well as to the immunologist. The Schick test, for example, has been of tremendous value in the determination of the individual's susceptibility to diphtheria toxin and there is no doubt that a similar susceptibility exists to other toxins, bacteria and proteins. When we study the susceptibility to infections clinically it is apparent that the susceptibility or immunity to disease is associated with definite anatomic and physiologic peculiarities. The older physicians were fully conscious of these pecu-

liarities They did not have our modern methods of diagnosis, not even the usual physical signs But the anatomic and physiologic peculiarities stood them in good stead in a diagnostic and prognostic way

Since we know the tremendous and important rôle that the endocrine system plays in the growth, development, and physiology of the individual as indicated by the characteristic endocrine syndromes, it is natural to hold the endocrine system responsible for the anatomic and physiologic peculiarities of the individual

This afternoon I shall present a group of cases of common medical diseases to illustrate the rôle that the endocrine system plays in these conditions Of course, in the absence of definite and measurable methods for the determination of the presence or absence of the specific secretions of the various endocrinous glands, we must rely largely upon purely clinical grounds for the determination of whatever endocrine manifestation is present in the patient Yet, the studies of the basal metabolism has developed at least one definite measurable method for determining disturbances of some of the glands for internal secretion The presence of any definite endocrine characteristic in a patient does not determine the etiologic rôle of the endocrine system in the particular disease under consideration If the endocrine system plays such a rôle at all, this can only be established by good clinical judgment, by weighing every possible etiologic factor, and thus determining what rôle the endocrine system plays in the disease Some patients show irreparable endocrine markings merely as the finished product of the rôle the endocrine system has played in the development of the individual This resultant endocrinous individuality may explain the individual's susceptibility to disease and may determine his immune reactions, although at the present time these peculiarities are no longer subject to therapeutic modification On the other hand, there are frequent instances where the non-endocrinous visceral symptoms of commonly known diseases mask the underlying endocrine disturbance Consequently, the patients are considered to be suffering from these visceral diseases On close

study, however, it becomes apparent that these visceral symptoms are merely part of a mild endocrine disturbance, and the recognition of the endocrine basis enables us to establish the disease entity and to put the patient under proper treatment.

A careful study of definite endocrine syndromes shows that many of the usual symptoms of these conditions are often absent. Furthermore, the different symptoms vary in the intensity with which they dominate the clinical picture. For example, in a case of hyperthyroidism the various symptoms may vary in intensity, some symptoms may be entirely absent, while others dominate the picture to such an extent that the underlying thyroid condition is entirely overlooked. In some cases the tremor stands out prominently, in other cases the tachycardia, in still others, the gastric symptoms, and at times the diarrhea or the psychic symptoms—fear etc.—may dominate the picture. It is therefore apparent that such patients may be considered as suffering from various conditions—from a gastric disturbance, a cardiac disturbance, etc. But a careful study of these patients will frequently elicit the presence of all the other symptoms of a hyperthyroidism. Many of the symptoms occur in a very mild degree, but all of them taken together constitute the thyroid syndrome, and treatment along these lines will give much better results than the mere symptomatic treatment of the various visceral symptoms. This is also true of myxedema, of pituitary disease, or of any other endocrine disturbance.

In many of the infections we have definite evidence of injury to various endocrine glands, such as the adrenals, for instance. This injury of the internal secretory glands may manifest itself in the course of the disease or after recovery by various symptoms. The recognition of the underlying cause for these symptoms may be of invaluable therapeutic aid. Furthermore, many of the complications in various infections may be the direct result of various endocrine injuries, and here, too, the recognition of the endocrine injury will enable us to avoid the complication or to treat it along rational lines.

Changes in the physiology of the patient frequently precede

the pathologic lesion. Consequently, many diseases manifest themselves by disturbance in function long before an organic lesion can be demonstrated. And since the endocrine system plays an important rôle in immunity, disturbed endocrine function may be the earliest sign of an infectious or other organic disease. For example, every clinician of large experience has encountered cases of hyperthyroidism followed by early pulmonary tuberculosis. And a great deal has been written about the differential diagnosis between tuberculosis and hyperthyroidism. It seems more than likely that this hyperthyroidism is really one of the earliest signs of a disturbance in endocrine function and is probably the clinical evidence of an effort to overcome the infection.

THE RELATION OF THE THYRO-ADRENAL APPARATUS IN GASTRIC NEUROSES

I wish to present a number of cases this afternoon that illustrate the rôle of the thyroid and adrenal glands in the so-called gastric neuroses associated with disturbances in the gastric secretion. The patients who present themselves to the physician with "stomach trouble" usually complain of more or less characteristic symptoms, all of which are referable to trouble in the right side of the abdomen and particularly to the right hypochondrium. In many of these patients by a careful study of the history and a thorough examination we can establish a definite lesion, such as a chronic appendicitis, gall-stones, or possibly an ulcer of the stomach or duodenum. (And here it is worthy of note that a diagnosis of a gastric or duodenal ulcer is made more frequently than is warranted by the pathologic findings.)

When we have excluded these definite lesions we find that the majority of the cases form a group in which we cannot state definitely whether they have gall-stones, gastric or duodenal ulcer, or appendicitis. Finally, on analysis of the gastric contents it is determined that they suffer from a disturbance in the gastric secretion manifested by a hyperacidity or by an anacidity or even by a complete absence of all the elements of

the gastric juice And the radiograms may show a gastropptosis, a visceroptosis, or a gastric atony

Now it is quite apparent that the mere secretory disturbance in the stomach is not really a disease but a symptom of some other underlying condition If we study these so-called gastric neuroses carefully we find that the symptoms constitute a definite clinical entity, and that these patients have more or less the same clinical characteristics in common Consequently, we can classify most of these cases, from a clinical and endocrine standpoint into the following three groups

1 The first group consists of cases which show at the time they come under observation definite signs of a mild form of hyperthyroidism or thyroid deficiency

This group of cases is more common than is usually appreciated The patients may show the signs of thyroid overactivity the tachycardia the tremors the nervousness They do not gain in weight and may even lose in weight Frequently enlargement of the thyroid gland may be present and even a slight or a moderate exophthalmos, and there may be an increased basal metabolism But all these symptoms are usually overshadowed by the dominant gastric symptoms and objective findings of secretory disturbance

On the other hand there are patients who show all the clinical evidence of thyroid deficiency they are drowsy sluggish mentally the skin is dry and scaly the hair keeps falling out there is a sparse growth of hair on the outer part of the eyebrow, there is a tendency to obesity, puffiness of the eyelids, and even the basal metabolism may be lowered But here again these symptoms are masked by the dominant symptoms in the right hypochondrium

2 The second group consists of cases in which the gastric symptoms are the earliest manifestation of a hyperthyroidism or a hypothyroidism which subsequently develops into the classical syndrome

This group consists of patients who complain of symptoms in the right hypochondrium with more or less the same symptoms as the others and with negative objective findings But when

they first come under observation they have very few symptoms referable to the thyroid gland, except nervousness, occasional tachycardia, and possibly a loss in weight. But as these cases are kept under observation they gradually develop, in a few months or within a year or later, several, and finally all the symptoms of a classical hyperthyroidism, as will be illustrated in two of the following cases, where after the presence only of gastric symptoms for months, there gradually developed tremors, loss in weight, excessive perspiration, enlargement of the thyroid gland, increased basal metabolism, and even exophthalmos. And the patients then showed the classical syndrome of hyperthyroidism as the illustrations show.

3 The third group comprises the patients who show the characteristics of the domination of the adrenals or of the thyroid in the endocrine physiology of the patient.

The patients in this group show clinical evidence objectively, and on careful study of their history that they belong to a group of individuals in whom the adrenal glands or the thyroid dominates the function of their endocrines. These individuals are called adrenotropes and thyrotropes. The adrenotropes occur mostly among males, while the thyrotropes occur more frequently in females. Since these glands are functionally very active in these patients, they are readily upset by physical and mental shocks, infections, or injuries. As a result the patients show evidence of what we might term "endocrinasthenia." If the adrenal is involved we might term the condition "adrenalasthenia," if the thyroid, "thyroidasthenia." As a result we get the clinical evidence of deficient activity of the gland involved, plus the signs of compensatory action of one or several of the other glands.

The adrenotrope has a tendency to excessive pigmentation. This is manifested by numerous brownish areas on the skin, mucous membranes, and teeth. (The pigmented spots are believed to be areas of compensatory chromaffin tissue on account of adrenal deficiency or injury, as in Addison's disease for instance.) They have an abundant growth of hair on the chest, on the back, on the abdomen, and extremities. The hair of the

scalp and rest of the body is inclined to be coarse, very curly and brittle. It is usually very dark in color except in those races where dark hair is usual when adrenotropic hair is inclined to be blonde or red. They are apt to have long-pointed canine teeth. They are subject to evanescent changes in blood-pressure, at times it is very high and at other times it may be abnormally low. They are usually very energetic, aggressive individuals who take life very seriously and are constantly under mental tension. They usually come of families subject to vascular diseases, arteriosclerosis, apoplexy, and hypertension. They have a predilection for diseases such as influenza, diphtheria, etc., which tend to produce adrenal injury.

This is one of the clinical types of patients who complain of gastric symptoms without evidence of organic lesions and in whom no definite diagnosis can be made. Because of the associated nervous symptoms they are diagnosed as gastric neuroses. Many of these patients have a hyperacidity which I believe in most instances is a temporary condition, as the hyperacidity may disappear just as readily as it came. The gastric symptoms are frequently accompanied by low blood-pressure. The entire clinical condition is probably part of a constitutional asthenia, the result of exhaustion of the adrenals, which we might term "adrenal asthenia." Since these patients are adrenotropes and their endocrine physiology is dominated by the adrenal glands these glands are the first to become exhausted by mental shocks or physical injuries.

We know that the adrenals are the great sensitizers of the sympathetic nervous system. Consequently, when adrenal insufficiency occurs functionally or organically, the result is lessened sensitization of the sympathetic nervous system. All the abdominal viscera are innervated both by the autonomic or vagus system and by the sympathetic system, and there is a reciprocal action between these systems. The diminished sensitization of the sympathetic system, therefore, produces a state of vagotonia characterized by the gastric symptoms, hyperacidity, etc.

In many of these patients mental shocks, nervous tension

and subsequent exhaustion precede the onset of the symptoms. We have evidence of the relation of the cerebral cortex and the adrenals, particularly the cortex (anencephalic monsters have a complete absence of the adrenal cortex). It seems, therefore, very probable that mental shocks, nervous tension and exhaustion, and psychic states may also play a rôle in the production of adrenal insufficiency in the adrenotrope as well as the toxins of various infections such as diphtheria and influenza. As a result the nervous and gastric symptoms are produced.

The thyrotropes are individuals most of whom are women, whose endocrine physiology is dominated principally by their thyroid glands. They are usually rather thin women, inclined to be tall, they rarely gain in weight, they have very fine, delicate hair, their teeth are usually in good condition, pearly white or bluish in color, and their eyes are usually bright. They are inclined to be emotional and they readily show the physical accompaniment of emotions, such as blushing, tachycardia, and nervousness, and they are subject to fears. They frequently suffer from chilblains and their hands get cold, clammy, and moist. Their symptoms may be aggravated at the time of menstruation and they frequently have amenorrhea and other menstrual irregularities. They have a tendency to suffer with sore throats and tonsillitis, from which they recover readily, as they do from other infections and the usual diseases of childhood, from which, however, they are relatively free. At times the thyrotropes, especially when they are suffering from symptoms, may show a slight tendency to obesity, falling out of the hair, dryness of the skin, etc.

Since the thyroid gland in these patients is probably the dominant gland in the endocrine physiology, it is highly sensitized and readily suffers from mental and physical shocks. As a result, we get symptoms of thyroid excitation or mild thyroid deficiency, frequently with dominant gastric symptoms of a functional nature associated with disturbance in the gastric secretion. And it is for these symptoms that many of these patients come under observation for a so-called gastric neurosis, which is really part of the general constitutional disturbance.

The roentgenographic findings in the patients of the groups I have described are more or less characteristic. I have had roentgenograms taken of the gastro-intestinal tract of all the frank cases of exophthalmic goiter and hyperthyroidism that have come under my observation. Nearly all of them have shown a gastropnoxis. With the exception of the cases that showed definite signs of thyroid deficiency, the cases in the groups described above showed a similar condition. The discovery of the gastropnoxis in the roentgenogram has often led to the explanation that the gastric symptoms were due to the evident mechanical condition of the stomach. I have seen these patients wearing belts and specially constructed corsets for years, but the mechanical condition of the stomach remained the same. Furthermore, there was no relation between the roentgenographic appearance of the stomach and the symptoms. The appearance of the stomach in the roentgenograph always remained the same whether the symptoms improved or not. Consequently, I believe there is no relation between the symptoms and the roentgenographic findings. Careful study of the patients in the above groups indicates that the gastropnoxis is part of their constitutional stigma. It is more than probable that an endocrine disturbance is responsible for this mechanical condition of the stomach. But whether it is due to a pituitary deficiency with resultant atony or not it is as yet difficult to determine. At any rate, in my experience it seems to be one of the characteristic objective findings in cases of hyperthyroidism in the adrenotopes and the thyrotropes. The gastric symptoms and the secretory findings in the stomach of these cases are probably the result of the endocrine disturbance of which the nervous symptoms, the secretory disturbance in the stomach, and the gastric symptoms are merely part of a general glandular difficulty which may be a full-fledged hyperthyroidism, an incipient hyperthyroidism or thyroid deficiency or an endocrinasthenia in an adrenotropic or thyrotropic individual. And it is within the realm of rational theoretic conception, though still subject to proof, that this endocrine constitutional basis may, given the proper irritants, be the fertile soil upon which

a gastric ulcer, duodenal ulcer, or cholelithiasis may be the terminal results

The therapeutic indications in these cases from an endocrine standpoint depends upon the group to which the patient belongs. Endocrine therapy is substitution therapy. If there is evidence of a *forme fruste* type of thyroid deficiency, the administration of thyroid extract in small doses or, better still, thyroxin gives excellent results. If there is evidence of hyperthyroidism or incipient hyperthyroidism, the patient should be treated not so much as a gastric case, but as a case of hyperthyroidism. The patient should be put at rest both physically and mentally and the diet should be like that of a hyperthyroid case. I have frequently obtained good results in these cases by the use of adrenal cortex. This is used on the basis that overactivity of the thyroid and adrenal medulla frequently go together. The function of adrenal medulla and cortex, however, are antagonistic to one another. Asthenia and pigmentation in Addison's disease are probably due to deficient activity of the adrenal cortex. These symptoms are of frequent occurrence in cases of hyperthyroidism. Consequently, the adrenal cortex is used to supply a deficiency in an attempt to overcome the overactivity of the adrenal medulla. This may be combined with pituitary extract and ovarian extract in females, depending on the constitutional indications of the patient.

In the adrenotropes the symptoms can be controlled at times with almost specific effect by the use of suprarenal extract. The thyrotropes are treated in the same manner as the cases of hyperthyroidism with gastric symptoms as indicated above.

Case I Hyperthyroidism Beginning with Gastric Symptoms
—K C, a young married woman of forty, came under observation in August, 1920, with the following history. For about two years following an attack of influenza she has been having pains in the epigastrium coming on usually after meals, accompanied at times by vomiting spells. About a year ago the symptoms became aggravated and she began to be very nervous. She was treated for stomach trouble all this time until about six

months ago, when she noticed that her eyes were becoming more prominent. This became more marked, she developed palpitation of the heart, and a few months later she noticed a slight enlargement of the thyroid. These symptoms have gradually increased and she has since developed attacks of profuse perspiration, cough, diarrhea, profound weakness, and tremors.

She had always been well before the onset of the present illness. Her menstruation began at thirteen and has always



Fig 147 —Case I, K. C., showing exophthalmos and goiter occurring one and a half years after persistent gastric neurosis

been regular, lasting at first about three days and later five. She has been married sixteen years and has had no children because she did not want any.

Her parents are alive and well, she has four brothers and sisters who are all well. There is no history of any thyroid condition or any other endocrine condition in her family.

The patient is a rather thin, middle-aged woman who is

extremely nervous and fidgety There is no rash on the skin, but there is considerable pigmentation about the neck and chest There is a moderate exophthalmos, a positive von Graefe and Stelwag sign The teeth are in excellent condition, pearly white in color, the tonsils are not enlarged There is a moderate enlargement of the thyroid gland The chest is normal in



Fig 148—Roentgenogram of stomach of Case I, K C, showing marked gastroptosis

shape and contour, the costal angle is acute The lungs are normal, the heart is not enlarged, but the rate is 130 and no murmurs are heard

Examination of the abdomen shows tenderness on pressure in the epigastrium with evidence of a marked gastroptosis, the lower border of the stomach extending way down to the level of the anterior superior spine of the ilium The blood-pressure

was systolic 174, diastolic 78. Roentgenographic examination showed a normal sella turcica, no enlargement of the thymus, no evidence of a substernal goiter, but a very marked gastroparesis.

The Goetsch test gave a very marked reaction. The pilocarpin test for vagotonia was negative. The basal metabolism was $+80$ per cent.

The symptoms gradually became worse, the loss in weight increased, the exophthalmos became more marked, she began to suffer with insomnia, she became delirious and the basal metabolism went to $+105$ per cent, and she developed into a fulminating case of thyrotoxicosis.

This patient began to suffer with gastric symptoms following an attack of influenza. Apparently at the onset there were no definite signs of hyperthyroidism. But since the patient subsequently developed a full-fledged case of hyperthyroidism even a thyrotoxicosis, it seems logical to consider the early gastric symptoms as the first signs of the hyperthyroidism. We can explain the origin of the condition on the basis of the influenza which preceded the onset. The influenza probably produced an injury of the adrenals, probably of the cortex, and the thyroid condition developed as a compensatory phenomenon.

Case II Hyperthyroidism Beginning with Gastric Symptoms—J. M., a middle aged jeweler of thirty-nine, came under observation in November 1920 with the following history: Ever since December 4, 1919, when he was held up at the point of a pistol in his store, though not injured, he has been complaining of gastric symptoms and nervousness. This began with pain in the epigastrium appearing about two or three hours after meals, which gradually grew worse and were accompanied by increasing nervousness. He was treated for the stomach condition all this time without any relief. About two months ago his nervousness increased, he developed occasional palpitation of the heart, and he noticed slight bulging of the eyes. About two days before he was referred to me, he took about eight 10-grain tablets of aspirin to relieve the severe pain in the stomach. The pain, however, became exaggerated and

he developed stiffness of the neck and back and muscular twitchings

He was never ill except for an attack of influenza about three years ago, he denied venereal disease

The patient is a heavy smoker and a very hard worker. He works about fourteen to sixteen hours a day. He has been married fourteen years, but his wife has had no children

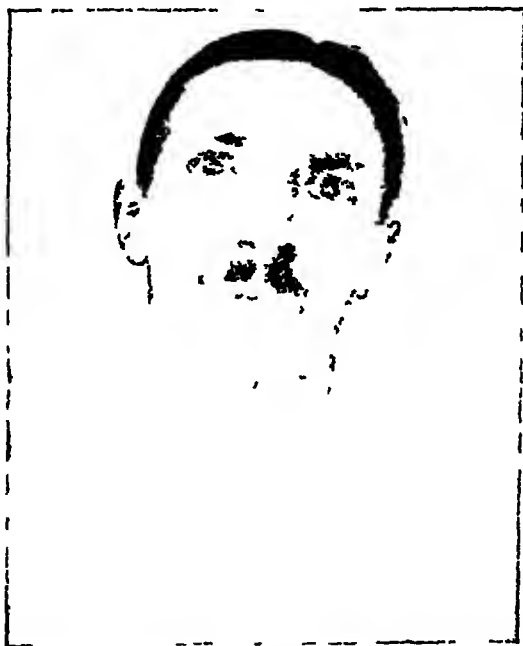


Fig 149—Case II, J. M., showing exophthalmos and thyroid enlargement occurring after two years of persistent "gastric neurosis"

The patient is a medium-sized man who is quite nervous and flushes readily. There is no rash on the skin, but there are a few pigmented spots on the back and chest. There is a notable absence of hair on his body and his beard is not very thick. The pubic hair is of the feminine type, the pelvis approaches the feminine dimensions, but his external genitals are normal.

There is a moderate exophthalmos, the pupils are round, equal, and they react to light and accommodation. The tonsils are not enlarged, the throat is congested. The thyroid is slightly enlarged. The lungs show no evidence of any abnormal changes. The heart is not enlarged, the rate is rapid, 100, but the sounds are regular, rhythmic, and of good muscular quality, and no murmurs are heard.



Fig. 150—Roentgenogram of Case II, showing marked gastrop-tosis
(Note that this cut is reversed)

Examination of the abdomen showed only tenderness on pressure in the epigastrium and evidence of a marked gastrop-tosis, the lower border of the stomach extending way down into the pelvis. The extremities showed marked twitching of the arms, rigidity, and a fine tremor.

The blood-pressure was systolic 115, diastolic 80. The basal metabolism was +45. The Goetsch test was positive.

Laboratory Examination—The examination of the urine showed a specific gravity 1022, no albumin, no sugar, and no casts. The blood count showed W B C 9000, polynuclears 62 per cent, large monoculears 20 per cent, small lymphocytes 18 per cent, and no eosinophils.

Roentgenographic examination showed a very marked gastropotosis and a small sella turcica.

This patient has been suffering with gastric symptoms and nervousness ever since he was held up. But since the condition gradually grew worse and was gradually followed by all the characteristic signs of a hyperthyroidism, it seems probable that the gastric symptoms were really the first signs of the hyperthyroidism. It is interesting to note the presence of the gastropotosis in this as in the other case. Another interesting feature of this case is the fact that the patient showed several signs of a slight dyspituitarism, the feminine pubic hair and feminine pelvis, the scanty hair growth, and the small sella turcica. This has been noted frequently in male hyperthyroid patients, and may bear a relation to the fact that hyperthyroidism is more common in females than in males. This patient was put on a rest cure, his diet regulated, and adrenal cortex and pituitary extract were administered. Within four weeks his gastric symptoms subsided, his hyperthyroidism improved, and his basal metabolism is now +14.

Case III Hyperthyroidism Beginning with Gastric Symptoms—B B, a young married woman, twenty-six years of age, was admitted to the Lenox Hill Hospital in July, 1920, complaining chiefly of pain in the stomach and vomiting, which began two weeks before admission. The pain is not characteristic, has no relation to meals, but it is situated in the right hypochondrium, it comes on just as frequently when the stomach is empty as after meals. Vomiting produces temporary relief, and is usually followed by nervous weakness. The sight of food would produce an attack of nausea and vomiting, the vomitus was always greenish in color, occasionally headaches followed the vomiting. The bowels were always constipated, and were relieved by enemata. Cathartics tend to aggravate

the symptoms She is very thirsty, and drinks large quantities of water because she thinks it is good for her

She had diphtheria, typhoid, and other diseases in childhood About a year ago she was in the hospital with very similar symptoms, which lasted for six months At that time the condition was diagnosed as a gastric ulcer, and the patient was operated upon, a gastro-enterostomy was performed, but the question of ulcer was doubtful

Menstruation began at thirteen, was always scanty, lasted about one day but regular, and occasionally accompanied by severe pain She had a miscarriage about three years ago

The patient is a young woman with cheeks flushed and quite nervous The scalp is covered with an abundant growth of fine chestnut colored hair There is a moderate exophthalmos of both eyes The nose and ears show no evidence of abnormal changes The teeth are pearly white and in excellent condition The throat is congested and the tonsils are small and ragged The thyroid gland is moderately enlarged The chest is symmetric, the expansion good The lungs show no evidence of abnormal changes The heart is moderately enlarged and beats very rapidly, although no murmurs are to be heard The costal angle is very acute

The examination of the abdomen shows marked tenderness in the right upper quadrant The lower border of the stomach extends about three fingerbreadths below the costal margin

The extremities show only a very fine tremor of the fingers

Laboratory Examination—The gastric analysis after an Ewald test-meal showed a free acidity of 57 and a total acidity of 83, with occasional leukocytes and a few starch granules Examination of the stools was negative The Wassermann reaction was negative

Radiographs of the gastro-intestinal tract show evidences of a gastro-enterostomy with a patent stoma and a gastropnoxis

The adrenal reaction showed a very marked tremor, the pulse rose from 96 to 130 and the blood-pressure from systolic 105, diastolic 80 to systolic 115 diastolic 70 The pilocarpin reaction showed no change in the pulse-rate but a flow

of 70 c.c. of saliva within half an hour after the injection of $\frac{1}{16}$ grain of pilocarpin

This patient was admitted to the hospital with gastric symptoms, and the only objective evidence of any gastric lesion was that of an old gastro-enterostomy with gastroptosis, and a marked hyperacidity, but on taking the whole clinical picture into account, we find the patient also shows evidences of hyperthyroidism. She has a large thyroid, she has a tachycardia, she has lost in weight, she has an exophthalmos, she has a fine tremor, she is highly neurotic, and she has a positive Goetsch test. The basal metabolism was not done, as we had no apparatus at the time. In other words, the patient has a clinical syndrome of hyperthyroidism, with a visceroptosis and a hyperacidity, and since we know that a great many cases of hyperthyroidism are accompanied by gastric symptoms, it is much more rational to assume that this patient is suffering from a hyperthyroidism with dominant gastric symptoms rather than from a so-called gastric neurosis with hyperacidity.

Furthermore, the patient was in the hospital with an apparently similar history about a year previous to the present illness. It therefore seems much more likely that the patient had the same condition at that time. However, we cannot gain any evidence from her previous history as to whether she had any thyroid symptoms at that time or not, but since she has them now and since the present condition is merely a syndrome of hyperthyroidism, it is probable that the syndrome a year ago was the same. Consequently, we conclude that this patient is suffering from hyperthyroidism with dominant gastric symptoms.

Case IV "Forme Fruste" of Thyroid Deficiency—E. C., a young woman, a stenographer, aged twenty-one, came under observation in June, 1920. She complains that for the last ten or twelve years she has been under weight, has lost appetite, is constipated, feels generally run down, and has lost "pep." She weighs about 100 pounds with her clothes on. Her hair has been falling out for a number of years. She has a postnasal discharge. She feels drowsy and tired, especially after eating

She does not perspire readily, and skin feels coarse and dry. She has a scaly condition of the face. No cough or expectoration. Has epigastric pains after eating. Had measles and mumps in childhood.

Menstrual history began at eleven years, regular, only lasts about five days and is very profuse. She feels irritable a few days before menstruation.

The patient is a rather thin young girl. The skin is dry and scaly, there are atrophic spots over the skin of the chest. There is no Sergeant's line. The scalp is covered with dry, coarse hair. The pupils are round, equal, and react to light and accommodation. The nose and ears show no evidence of any abnormal changes. The mouth and teeth are in excellent condition. The throat is congested.

The lungs and heart show no evidence of abnormal changes. The abdomen shows little tenderness on pressure in the epigastrium, the stomach is dilated, the lower border extending to about three fingerbreadths below the lower level of the navel.

Roentgenograph of the gastro-intestinal tract showed no evidence of ulceration or malignancy in the stomach or duodenum.

The urine examination shows a rather specific gravity, with an increase in the phosphates, but is otherwise negative. The gastric analysis shows an absence of free acidity and a total acidity of 12. The blood examination showed polynuclears, 46, small lymphocytes, 46, large lymphocytes, 8, eosinophils, none.

The pilocarpin reaction showed a slight change in the pulse and a secretion of 55 c c in half an hour. The adrenalin reaction was negative.

This patient complains chiefly of gastric symptoms, but on careful examination it seems evident that there is no definite evidence of a gastric lesion, and that the gastric symptoms together with the other general symptoms are part of a mild thyroid disturbance. She was put on thyroid extract, with gradual improvement.

Case V. Thyrotrope with Symptoms of Thyroid Irritation with Dominant Gastric Symptoms—F H, a young married woman of twenty-nine, came under observation in August, 1920,

with the following history She was perfectly well until about five years previously, when she began to suffer with attacks of indigestion These attacks are quite characteristic They occur about half an hour after meals and last for a week at a time For the last few years, however, she has had an attack about every week She describes the attack as if a rock was resting over the sternum, and this produces severe, intense pain which extends up to the left shoulder, and is followed by severe belching, which, however, does not relieve her She feels as if vomiting would relieve her, but she does not vomit About three years ago she was under treatment for this condition, and her physician advised her to have her appendix removed, which was done At the operation it was found that the appendix showed very little if any lesion save an occasional adhesion, and that she had a movable colon and a general visceroptosis Following the operation, however, she did not improve As a rule, she is constipated, and the violent cathartics which she occasionally takes make her feel worse Celery, apples, or grapes are the types of food that are particularly bad for her Eating candy or fruit between meals usually brings on an attack She has had a number of protein sensitization tests made, and it was found that she is sensitive to celery, lettuce, and spinach She does not perspire readily She complains that her skin is dry and her feet and scalp are dry For the last year her hair has been falling out, and this has increased in the last three months She is and always has been very thin, and does not gain in weight readily She weighs about 90 pounds She gets tired very easily

She had a light attack of measles, pertussis, and croup during childhood Has never had any hay-fever She catches cold very easily, but gets rid of it quickly She had pneumonia and bronchitis at the age of two She began to menstruate at the age of sixteen, and has always menstruated regularly, duration six days, not painful, however She always feels cold and her hands and feet are always cold

Her father is alive and well He had an attack of influenza which "settled at the base of his brain," but is well now at

fifty-two years of age Mother is alive and well at fifty-one Mother has no history of stomach trouble, no history of asthma, hay-fever, goiter, or pituitary trouble in the family She has five sisters, all of whom are well Her paternal grandmother died at the age of seventy-five of cancer, and her paternal grandfather died of a chronic cough at the age of eighty-three Her maternal grandparents died of old age

Examination showed a thin, very nervous young woman of medium stature, the skin dry and scaly, especially at the lower part of the abdomen and chest There is a tendency to callous formation on the tips of the fingers and toes There is no Sergent's line, and there is no unusual distribution of hair She has very fine, delicate hair The skin is rather dry, the eyes show a slight exophthalmos, the face flushed the pupils dilated The teeth are in excellent condition and they have a very fine bluish-white color and show no evidence of decay The nose is Grecian Examination of the nose showed hypertrophied middle turbinates on the right side Tonsils very small, throat slightly congested The chest is narrow, the costal angle is acute The lungs and heart are normal except for a marked tachycardia, the pulse-rate is 130 The oculocardiac test is positive, pulse reduced to 110 and slight perspiration of the hands (indicating a vagotonia) There is tenderness on percussion over the spine of the eighth thoracic vertebra The abdomen is normal in shape and contour There is a tenderness of the entire epigastrium and in the left upper part of the abdomen The left kidney is movable The stomach is markedly dilated the lower border extending to about two fingerbreadths below the border of the navel There is slight tenderness on pressure on both lower quadrants of the abdomen Liver and spleen not enlarged Otherwise the examination is negative

The urine examination shows evening specimen 1030, no albumin, no sugar Morning specimen 1025, no albumin, suggestion of sugar Microscopic examination of both specimens negative, only a moderate number of the epithelial cells

The gastric analysis showed a free acidity of 24, total, 50

Moderate number of starch cells well digested The Goetsch test was positive *The basal metabolism was +28 (Jones' apparatus)*

The patient is evidently suffering from gastric symptoms especially referable to the right upper hypochondrium There is nothing in the history or the physical findings at all indicating any organic lesion, consequently we must include this patient in the group of the so-called gastric neuroses

A study of the history shows that this patient was operated upon for appendicitis, and an appendix was removed which did not show much evidence of any pathology The patient was told she had visceroptosis and she wore a belt for years without any improvement in her condition, and the physical examination shows that the anatomic situation of the stomach has evidently not been materially changed It seems likely, therefore, that the patient has had this visceroptosis for years, and that it is merely a part of her anatomic individuality On the other hand, the patient shows stigmata of the domination of the thyroid gland in her physiology, she is thin, she is neurotic, she suffers from fears, she loves detail work, she is aggressive and is an intense and active worker The cold hands, the slight exophthalmos, and the high blood-pressure all corroborate the domination of the thyroid gland in her physiology The visceroptosis is another stigma of the condition The symptoms she is suffering from are clearly referable to these endocrine glands The patient is a thyrotrope suffering from thyroid excitation, as is indicated by her symptoms and increased basal metabolism, and she has been treated accordingly—put on a rest cure, given adrenal cortex—and gradually the symptoms subsided and the pain disappeared, she began to gain in weight, her nervousness cleared up, but her visceroptosis remains and her kidney is still floating She is, however, able to do her work, and functionally she is apparently perfectly normal, although anatomically she has certain stigmata

Case VI Thyrotrope with Gastric Symptoms—O M, a young governess, thirty-three years of age, came under observation in May, 1920, complaining that for the last five weeks she

has lost her appetite and is constantly belching gas. She was under treatment by a prominent gastro-enterologist, but her condition did not improve. In a few weeks before she came under observation she had lost 4 or 5 pounds in weight. She does not vomit. She has had slight epigastric pains for two days. The pain comes on right after eating. The belching of gas and abdominal distention is accompanied with constipation. The hair has been falling out in the last year. The skin is dry and scaly, and she does not perspire readily.

Three years previously she was treated for a gastric ulcer, the chief symptoms of which at that time were a heavy feeling of the abdomen and constant belching of gas, but no vomiting and no characteristic pain. The diagnosis of ulcer was not verified however, by the roentgenographic findings.

The patient is very nervous, and following her illness of three years ago she has been complaining steadily of pains and weakness in the calves of her legs.

She had scarlet fever as a child, influenza nine years ago.

Her menstrual history is normal except that for the last three years the menstruation has been painful and more frequent, lasting three or four days at a time.

Her father died of old age, her mother died of eye disease. She has two sisters, both of them living and well.

The patient is a rather thin young woman, and highly neurotic, rather tall, with dark complexion. The skin is rather dry and scaly. There are occasional pigmented spots over the abdomen and neck. The pupils of the eyes are round, equal, and react to light and accommodation, there is a slight exophthalmos of both eyes. In the mouth the teeth are in fairly good condition but they are short and have flat surfaces, the throat is slightly congested. In the neck the thyroid is not enlarged. There are no other glands felt.

The chest is normal in shape and contour, the lungs are normal. The heart is not enlarged, but the pulse-rate is a little rapid. Blood-pressure systole 120, diastole 75. The costal angle is very acute. There is slight tenderness on pressure over the left lower quadrant of the abdomen and in the right

hypochondrium, and there is a marked gastropnoxis, the lower border of the stomach being only a few fingerbreadths above the symphysis pubis

The urine examination was negative The blood examination showed polynuclears, 58, small lymphocytes, 18, large lymphocytes 20, eosinophils, 4



Fig 151 —Roentgenogram of Case VI, O M , showing marked gastropnoxis

The gastric analysis showed free HCl, 43, total acidity, 74 The radiogram of the gastro-intestinal tract showed a tremendous gastropnoxis, the greater curvature of the stomach extending way down to the pelvis *The basal metabolism was +18*

This patient came complaining chiefly of gastric symptoms, and was at one time treated for a gastric ulcer without any relief On physical examination she shows no evidence of an organic lesion and all the stigmata of a thyrotrope with a marked

gastroptosis The present condition is probably due to thyroid irritation She was put on a proper diet and given small doses of suprarenal extract She has gained about 16 pounds and feels much improved

Case VII Thyrotrope with Gastric Symptoms—N W, a blond middle-aged woman, about forty years of age, came under observation on August 28, 1918, complaining chiefly of gastric symptoms At that time she stated that two years previously she began to suffer from gastric eructations all day long There was no definite pain and no vomiting Two weeks before she consulted me she had an attack of continuous gastric eructation, lasting for seven hours There was no headache She was always nervous, she never gained in weight, her appetite was good For the last few months she had had cramplike pains after eating She has always perspired very little She complained of constant fears

The only points in the past history of importance were that in 1904 she had had an attack of so-called intestinal obstruction which was relieved by catharsis, and she had had typhoid fever eighteen years previously, at which time she was sick for three months but had no complications Her menstrual history had always been normal, although for the past few years the flow had been excessive and she had been quite nervous just before the period during which time she suffered from so-called flushes She had been married for about fifteen years and had never had any children

Physical examination at that time showed a highly neurotic, nervous woman, with slightly cyanotic hands She was constantly talking and active and changing from subject to subject The examination of the skin showed no abnormalities The scalp was covered by an abundant growth of blond hair, although it was quite dry Her pupils were round and equal, somewhat dilated but no exophthalmos was present The nose and ears showed no abnormal changes In the mouth the teeth were in excellent condition—bluish white in color and showing very little evidence of decay The throat was slightly congested

The examination of the chest showed normal lungs The

heart was not enlarged, but the rate was quite rapid and no murmurs were heard. The pulse also was quite rapid. There was no evidence of arterial thickening. The blood-pressure was systolic, 150, diastolic, 80.

It was only when we came to the abdomen that any positive physical findings were present. These consisted of a marked visceroptosis, the lower border of the stomach extending below the level of the navel, and the right kidney was movable.

The examination of the stomach contents showed a moderate increase of free hydrochloric acid, otherwise negative. The urine examination showed a specific gravity of 1018, no albumin, no sugar, no indican, and microscopically, only an occasional white blood-cell and epithelial cell.

Roentgenograph of the gastro-intestinal tract showed only a marked gastropnoia.

The adrenalin reaction for sympathicotonia was negative. The pilocarpin reaction was positive.

Basal metabolism +32.5

The patient complained evidently of a gastric lesion, but there was nothing found to indicate that she had a gall-bladder lesion or an ulcer of the stomach, and she had what is ordinarily considered a gastric neurosis with a certain amount of secretory change and visceroptosis. On the other hand, the failure to gain in weight, the constant fears, the emotional reaction and flushes, the tremors, and the high blood-pressure, the increased basal metabolism were all indications of thyroid excitation with dominant gastric symptoms in a thyrotrope of which the visceroptosis and floating kidneys were also the markings.

The patient came again for observation about a year later, complaining of swollen ankles, no headache, occasional spots before the eyes, no loss in weight, and an exaggeration of the original gastric symptoms. The findings at this time were the same as those of the year before, except that the skin was dry and she had a falling out of the hair, in other words, a certain degree of thyroid deficiency.

Case VIII Adrenotrope with Gastric Symptoms—B. F., a middle aged married man of forty-two, came under observation

in October, 1920, with the following history For the last eight years he has had pain in the epigastrium extending around both upper quadrants of the abdomen to the back The pain is usually worse after meals and is relieved by drinking hot milk or hot water The pain does not radiate toward the shoulder He has lost considerable weight since the onset of the illness He has occasional frontal headaches, he feels nervous, his legs feel weak, and he has occasional palpitation of the heart

He has never been ill before the onset of the present illness He does not smoke or drink His father died a year ago of an apoplectic stroke, his mother is alive and well

The patient is a rather tall, thin man There is no rash on the skin, but there are a number of pigmented moles on the back and there is a very profuse growth of dark hair over the chest, abdomen, back lumbar region, upper and lower extremities The scalp is covered by an abundance of dark curly hair and his beard is very thick The eyes have a slight Mongolian slant, the pupils are round, equal and they react to light and accommodation The nose and ears are normal The teeth are in poor condition the front incisors have a flat surface and the canines are long and pointed, the tonsils are not enlarged The



Fig 152—Case VIII, B F, adrenotrope with gastric symptoms, showing extensive hair distribution of chest, abdomen, and extremities

thyroid is not appreciably enlarged The chest is normal in shape and contour and the costal angle is acute The lungs are normal, the heart is not enlarged, the rate is about 100, and no murmurs are heard The blood-pressure is systolic 105, diastolic 80

Examination of the abdomen shows only tenderness on pressure in the epigastrium There is ptosis of the stomach, the lower border extends to about midway between the level of the navel and pubis The extremities are normal

Laboratory Examination—The urine had a specific gravity of 1020, it showed no albumin, no sugar, or casts The analysis of the gastric contents after an Ewald test-meal showed a free HCl 62, total acidity of 83 The blood examination showed W B C 8000, polynuclears 64 per cent, small lymphocytes 27 per cent, large mononuclears 16 per cent *The basal metabolism was +22 per cent* The Goetsch test was negative

Roentgenographic examination showed only a marked gastropptosis, but no evidence of a gastric or duodenal ulcer

This patient shows the constitutional characteristics of an adrenotrope an aggressive temperament, a history of vascular disease in his family, extensive hair growth, pigmentation, and long-pointed canine teeth The nervousness and the low blood-pressure indicate an adrenal asthenia, while the gastric symptoms are probably due to a vagotonia, also the result of adrenal insufficiency

The patient was put on a rest cure, his diet was modified, and small doses of suprarenal extract were given The gastric symptoms have gradually subsided, his general condition has improved, and he has gained about 9 pounds in weight

THE RELATION OF THE PITUITARY TO ADOLESCENT "EPILEPSY" AND NOCTURNAL ENURESIS

This afternoon I shall present a number of young adolescent patients suffering from "epileptic" attacks and nocturnal enuresis alone or together I shall attempt to illustrate the rôle of the endocrine system and particularly the pituitary gland in these

conditions To elucidate the problem I shall first discuss briefly the salient points about the pituitary gland It is, of course, well known that the pituitary gland consists of two parts an anterior lobe of glandular structure and a posterior lobe consisting principally of chromaffin tissue, with a pars intermedia between the two The anterior lobe plays an important rôle in the growth and development of the bony and skeletal structures of the body and later of the genitals The posterior lobe is closely related with the function of the genitals, with sugar tolerance, and helps to maintain the tone of involuntary muscles, notably the uterus and the intestines

Overactivity of the pituitary, particularly the anterior pituitary, produces the characteristic picture known as acromegaly Acromegaly, however, is not really a disease It is merely a condition which records, by the characteristic enlargement of the extremities and of the hands, by the prominent supra-orbital ridges, by the broad nose, by the prognathism, by the increased interdental spaces by the tastes and mental attributes, the fact that here is an individual in whom the pituitary gland was unbridled in its power to regulate growth and development There are many individuals, however, who show mild degrees of pituitary overactivity not to an extent that may be called acromegalic, but who have rather characteristic broad features, perhaps disproportionate extremities, early ossification, characteristic teeth etc Such an individual we may term a "pituitrope," to indicate that the pituitary gland has played a dominant rôle in his endocrine physiology He often has other characteristics to indicate this rôle, such as fondness for music, characteristic appetite, etc, characteristic disease susceptibilities, to arthritides, to gout, to syphilis, etc (the latter probably due to the rather active genitals) But all these markings and susceptibilities are fixed and are probably not amenable to treatment

Trohlich's disease, or adiposogenitalis, is the reverse condition of acromegaly, and is probably due to deficient secretion of both anterior and posterior lobes of the pituitary Since the pituitary regulates bony and skeletal growth and development

lessened activity of the pituitary is manifested by deficient bony growth and by deficient genital development. If the dyspituitarism occurs before complete adolescence the bony and genital stigmata are manifest, but if it occurs after adolescence only the genital changes are manifest. The faulty genital development which is present both in the pre- and post-adolescent types consists of failure of the genitals to approach their adult characteristics associated with the secondary characteristics of the opposite sex. In males the skin is smooth and soft, there is a scanty growth of beard, the breasts are large, the pubic hair has a straight upper border, as in the female, and there is a tendency to increased deposit of fat around the body and over the buttocks and the pelvis approaches the female type, there is delayed ossification of the epiphyses, and there is a general lack of muscular tone. In the female, on the other hand, the genitals are infantile in type, the skin is coarse and there is a greater tendency toward hairiness, a tendency toward the growth of a beard, the breasts are small and atrophic, the bony prominences are more marked, and the pelvis has more the measurements of the male, the pubic hair assumes the masculine pyramidal border, and there are menstrual disturbances, such as delay in the beginning of menstruation, amenorrhea, sterility, etc., and lack of muscular tone.

Roentgenograms of the skull shows in the classical cases the large sella turcica in the acromegalic and the small one in the dyspituitary case.

In adults a classical Frohlich syndrome minus the bony characteristics may occur suddenly, usually associated with the focal symptom, bitemporal hemianopsia, as the result of a pituitary tumor.

Between a classical case of dyspituitarism and the normal individual there may be many degrees of pituitary deficiency. The cases may be characterized only by dwarfism, they may occur without adiposity or with very slight faulty genital development.

Since normal genital development is dependent upon normal function of the pituitary it becomes almost an endocrine avia

that defective genital development indicates in most instances dyspituitarism. As a rule, this genital development does not occur alone, but on careful examination other signs of dyspituitarism may usually be found. The defective development of the genitals may occur to a very slight degree, consisting only of a feminine pelvis with feminine pubic hair, but the genitals may be apparently normal and functionate normally, or the patient may be sterile. On the other hand, the penis may be small and the testicles may be undescended. I believe undescended testes should be regarded as a stigma of dyspituitarism. For in development of the testes two things occur, normal development and descent into the scrotum, through the inguinal canal, and a failure of the inguinal canal to occlude may also be regarded as such a stigma. If there is defective development of the testes not only will the testes be small and atrophic, but they will also fail to descend completely into the scrotum. And it is well known that undescended testes are usually atrophic testicles (How futile from a functional standpoint is therefore the operation to anchor it.) But the extent of its descent has, however, no relation to the functional ability of the undescended testicle. I have seen testes that were almost in the abdominal wall be more useful functionally than those that were almost entirely in the scrotum. The function is dependent on the degree of atrophy. Hypospadias may be regarded as another stigma of dyspituitarism.

In females dyspituitarism is characterized not only by the bony and skeletal changes, but by the evidence of defective genital development. This, as in the male, may only be very slight or very marked, with any number of gradations between. I have seen cases with a masculine pelvis and complete absence of the uterus and adnexa. The more common types, however, show an infantile uterus, with complete amenorrhea, or periodic amenorrhea, or sterility, or one child sterility, etc., together with many of the skeletal changes. I believe the so-called rachitic pelvis in most instances, without a history of rickets, is really a stigma of dyspituitarism. These patients are usually stout, the so-called rachitic pelvis is really a masculine pelvis. During

labor these patients have uterine inertia and they usually have no milk in the breast—all pituitary stigmata

An acromegalic individual may subsequently develop symptoms of dyspituitarism, probably the result of the failure of a large pituitary to erode the sella turcica, with resultant pituitary atrophy

The characteristic pituitary markings of an individual, and the same holds true for all endocrine stigmata, are usually transmitted to the children. The factors that influence heredity, however, are very complex, but the point that is of interest in this discussion is the fact that the specific over- or under-activity of an endocrine gland is not transmitted, but only the dominant gland is. For example, an acromegalic may give birth to dyspituitary dwarfs or to dwarfs and acromegalics. A dyspituitary dwarf, if not sterile, may give birth to an acromegalic, a thyrotrope may give birth to a cretin, etc.

The patients I wish to present are adolescent boys who came under observation for more or less the same symptoms: mild attacks of epilepsy, fainting spells, and nocturnal enuresis. The history given was usually that the boy had attacks of fainting spells during which he fell to the floor and remained unconscious for five to fifteen minutes, followed by drowsiness. Occasionally they would have a mild "fit," with twitching. Although they varied in age from eleven to seventeen years, they would still wet the bed at night. Careful examination of these patients failed to reveal any evidence of any visceral disease, and a thorough examination of the nervous system failed to reveal any evidence of organic disease of the nervous system. A diagnosis of idiopathic epilepsy and nocturnal enuresis was made, and they were referred for endocrine investigation.

If we study cases of classical dyspituitarism or Frohlich's syndrome in adolescent children it is frequently found that nocturnal enuresis, fainting spells, "fits," and mental backwardness form part of the clinical syndrome. When we examined the boys who came under observation because of these symptoms we found that they showed signs of dyspituitarism, though in some cases not very marked, one boy was a classical Frohlich

type, others were mild cases of dyspituitarism, and one showed acromegalic characteristics with dyspituitary symptoms. Consequently it was rational to consider these patients as cases of dyspituitarism in which the dominant symptoms were the fits, the fainting spells, and the enuresis.

Now as to the explanation of the symptoms, the nocturnal enuresis can be readily explained. Since the enuresis is physiologic in infancy and since dyspituitarism is characterized by faulty development, it is natural for some of the early physiologic characteristics such as the enuresis to persist. The other symptoms cannot be explained so readily, but the fact that the only objective findings are those of dyspituitarism and since the same symptoms occur frequently in classical Frohlich cases, it is logical to consider the whole picture as dyspituitarism. This, therefore, presents a guide for endocrine therapy which consists of feeding these patients whole pituitary gland, and very frequently with excellent results.

To emphasize the salient features of constitutional pituitary markings, I shall first present a few classical pituitary cases and then demonstrate the others indicating their pituitary markings.

Case I Acromegalic with Supervening Dyspituitarism —
M A, a young married man, twenty-eight years of age, has been married three years, has had no children. His wife was examined by several gynecologists and found to be normal. The patient himself was examined by his family physician, who found no spermatozoa in his semen. He has been gaining weight steadily, especially since he was married. He has had headaches occasionally since the age of sixteen, these were usually frontal and temporal in character, and occasionally on the top of the head. He has had occasional dizzy attacks since 1916.

In July 1916, while on the Mexican border with a National Guard Regiment, he had a severe gastro-intestinal attack. His previous history is simply that at the age of three his face was infected, leaving an extensive scar and his teeth have decayed readily since then. "The teeth decay from the inside" and get loose, and he pulls them out very readily. Otherwise his history

is negative He has been an excellent worker and has led a rather inactive sexual life He does not care for alcohol, does not smoke, for smoking makes him very dizzy He is very susceptible to alcohol, one glass of beer makes him very drunk

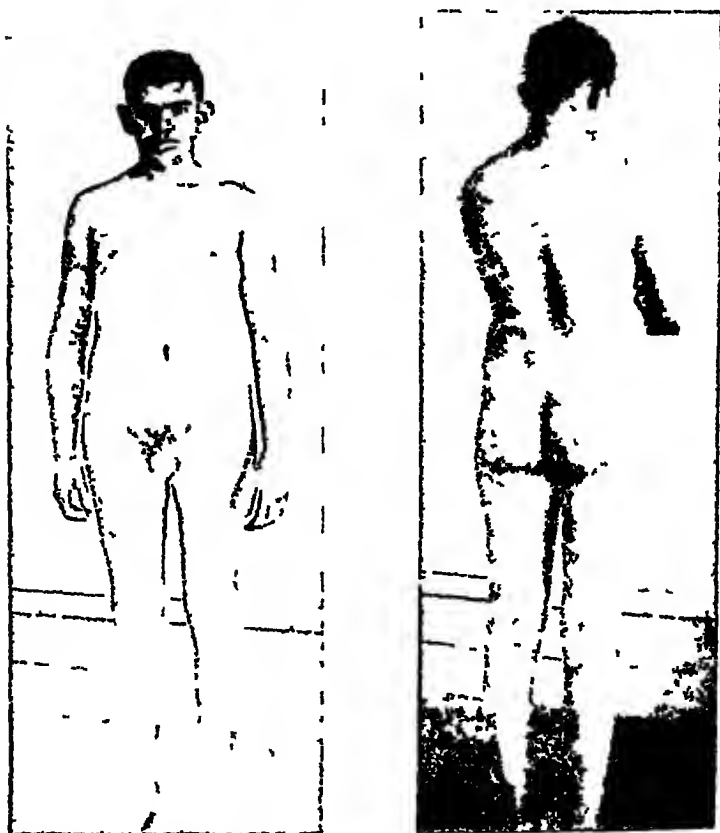


Fig 153 —Anterior and posterior view of Case I, M A , of acromegaly with dyspituitarism Note the broad pelvis and the feminine pubic hair

Both parents are alive and both very tall Has four brothers and four sisters, all tall, and very strong and athletic

The patient is a very tall, blond young man, he has a broad nose and square jaw, and prominent supra-orbital ridges He

has a scar on the inferior maxilla. The teeth are in very poor condition, the upper incisors and nearly all the front teeth are missing, the lower teeth are in poor condition, and there is an increase in the dental spacing between the teeth. The tonsils are submerged.

The skin is very soft and delicate, and shows no pigmentation, and there is a great sparsity of hair both on the face and over the body, he shaves only occasionally. There is no



Fig 154—Roentgenogram of skull of M A, showing large sella turcica

Sergent's line. The thyroid is not enlarged. The chest is broad but the costal angle is rather wide. The heart and lungs are negative.

The abdomen is pendulous, the pelvis is feminine in shape and width, the pubic hair is feminine in character and distribution. The testes are very small and atrophic.

The extremities are long and out of proportion to the torso. The pulse is 68. The blood-pressure is systolic, 140, diastolic, 80.

Laboratory Examinations—The urine is negative. Blood count polynuclears, 57, small lymphocytes, 32, large lymphocytes, 11.

The roentgenogram showed the sella turcica to be very large and broad.

This patient shows the characteristic pituitary markings. He has the characteristic stigmata of acromegaly. Subsequently there has supervened signs of pituitary deficiency, namely, the genital atrophy and the sterility.

Case II Frohlich's Syndrome with Epileptic Fits and Nocturnal Enuresis—S. K., a boy of thirteen years, came under observation in October, 1920, complaining that for the last four years he had been having fainting spells, which came on in attacks. At first the attacks would occur every two or three weeks, now they occur almost every week. The attacks come on suddenly, he becomes dizzy, has pain in his stomach, in the neck, and eyes, and falls to the floor unconscious, and occasionally has a real convulsion. At times he has periodic headaches, without real fainting spells. Usually before the attack comes on he has supra-orbital headache. Otherwise there is nothing in the history that is at all relevant.

The boy still goes to school, he has never been bright, but since the occurrence of the attacks he has not been at the head of his class as he was formerly. He had three attacks of diphtheria in three consecutive years, the first time at the age of three, then at four and five. Had pneumonia at the age of six. Had measles in infancy. Had a normal birth, but, as his mother expressed it, he "looked like a fish at first," but this physiognomic feature subsided very soon. He began to walk at the age of two and a half years. His teeth began to appear at the age of two years. He is very fond of sweets. He still has nocturnal enuresis.

His father is alive, but has "stomach trouble." His mother is alive and well. There is one sister, younger than the patient, ten years of age, who is perfectly well except for a chronic rash on the skin.

The paternal grandparents are alive, the grandfather is seventy, the grandmother, seventy-one. The grandfather has

cardiac trouble. He has one paternal uncle and one paternal aunt, both perfectly well. His maternal grandparents died in Austria during the war. The boy's mother has three brothers who are perfectly well.



Fig. 155—Case II, S. K. classical Fröhlich type of dyspituitarism complaining of epileptic attacks.

The boy is rather tall, inclined to be stout, and has a very high-pitched voice. His face is smooth and well filled out, resembling that of a girl; he has beautiful red cheeks and blue eyes. The pupils are round, equal, and react to light and accommodation. In the mouth the teeth are very small and the lateral incisors are rudimentary and pointed. The tonsils

are large, submerged, and congested. The skin is soft, smooth, and delicate, resembling that of a girl, and there is a very faint subcuticular network of redness under the skin. The hands are slightly cyanotic, and there are a number of dilated veins under the skin of the chest and abdomen.

The lungs and heart are normal. The breasts are enlarged, the nipples are prominent. The abdomen shows an increased amount of subcutaneous fat, and the abdominal wall is pendu-



Fig 156—Roentgenogram of skull of Case II, S K, showing small sella turcica

lous and overhangs the groins. There are numerous longitudinal striæ in both groins and in the suprapubic region. The abdominal viscera are normal, the pelvis is broad and feminine in character. The genitals are very small and the pubic hair is very scant, and the suprapubic fat resembles the mons veneris. There is a very small rudimentary penis, and the median scrotal ridge is inverted, and the testes are very small and atrophic.

The lower extremities are adipose, and he has flat-feet.

The roentgenogram of the sella turcica shows a very small rudimentary sella, and the roentgenograms of the hands show delayed ossification of the epiphyses

Basal metabolism -12 per cent

This patient complains chiefly of the so-called fainting spells, and occasional nocturnal enuresis. The fainting spells are probably a mild form of epileptic attacks



Fig 157 —Roentgenogram of hands of S K, Case II, showing delayed ossification of epiphyses

On physical examination, however, the boy shows very marked genital atrophy, and all the secondary sexual characteristics are feminine in character. In other words, the genital atrophy, the feminine sexual characteristics, the adiposity and the delayed ossification of the epiphyses are merely signs of a pituitary deficiency, which is corroborated by the small atrophic sella turcica. Consequently, the enuresis and the fainting spells are associated with evidences of dyspituitarism, and we have, therefore, sufficient reason to explain the epileptic attacks and the enuresis on the basis of pituitary deficiency. The

patient is still on pituitary feeding and the attacks have markedly lessened in frequency and severity, while the enuresis has completely disappeared

Cases III, IV, V Three Brothers with Hereditary Dyspituitarism—F K, young man of twenty-four, L K, aged seventeen,



Fig 158—Cases III, IV, V, F K, L K, and J K Three brothers showing hereditary dyspituitarism

J K, aged fifteen—three brothers, who came under observation in March, 1920, because their mother noticed that ever since birth these boys had not developed properly, and the younger two would get fainting spells

They were normal at birth, but L K had not begun to walk

until the age of two They were always well behaved never given to much mischief They were all very susceptible to warm weather and did not stand cold very well, and always had cold feet They got tired easily, and they did not perspire readily The youngest of the three has a tendency to develop headaches in warm weather, and until a few years ago he had nocturnal enuresis

They had the usual illnesses of childhood and the youngest had scarlet fever, but the others did not None of them smoke, and they do not care for tobacco

There are four older brothers who are all perfectly normal The father died of an alcoholic gastritis, He was a periodic drinker at first and later on became a constant drinker Alcohol was largely responsible for his death The mother is living and fairly well She is a very thin woman

Examination showed the following F K is 5 feet, 2 inches L K is 4 feet, 9 inches J K is 5 feet, 1 inch

None of them have any growth of hair on the face or body L K has prominent supra-orbital ridges The skin is soft, smooth, and not covered by hair No glandular enlargement The thyroid is not enlarged The teeth of all three show overlapping in both upper and lower sets They are all freckled The lungs and hearts of all three are sound The genital glands are all small and rudimentary and there is a very scant growth of pubic hair

The roentgenograms show very diminutive sella turcicae

The blood-pressure was as follows F K, systolic, 110, diastolic, 65 L K, systolic, 100, diastolic, 60 J K systolic, 90, diastolic, 55

The blood-sugar was within normal limits in all three

Basal metabolism F K +6 per cent L K -8 per cent J K +10 per cent

The roentgenographs of their chests showed no enlargement of the thymus

These three brothers show the characteristic markings of pituitary deficiency—the feminine character of the skin of the pelvis, the lack of development the scant hair, the stunting

in growth, they are all undersized, and the marked genital deficiency—all of which are evidences of pituitary deficiency, which seems to be corroborated by the roentgenographs of the skull, seems to be diminutive sella turcica

It is of interest to account for this congenital dyspituitarism, with the secondary markings. Consequently, we studied the markings of the mother, and found that though she had no

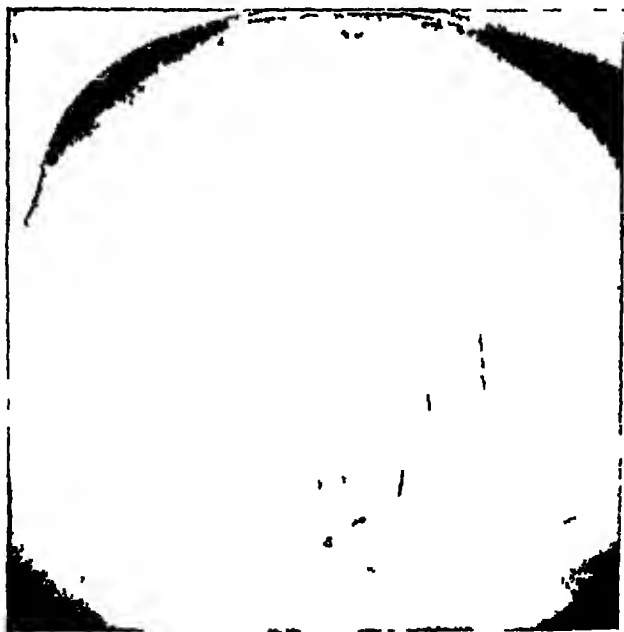


Fig 159 —Roentgenogram of mother of Cases III, IV, V, showing small sella turcica

genital atrophy, she nevertheless showed very marked overlapping teeth, and a diminutive sella turcica. Consequently, we assumed that the mother had a very small pituitary which, however, was not of a sufficient degree to produce genital atrophy. The boys evidently inherited these peculiar maternal markings, since they showed the pituitary characteristics and the same characteristics of the teeth. In the beginning of their par-

ental married life the father's characteristics were evidently dominant, since the first four children are apparently normal. But since the father was alcoholic his dominant characteristics became weakened and later the mother's characteristics became dominant, as is indicated in the last three children. But since genetic characteristics become intensified in succeeding generations, they have shown, in addition, the secondary genital changes.

Case VI Case of "Epileptic Fits," Nocturnal Enuresis, and Backwardness, with Dyspituitary Markings—M Z, a boy of eleven years, came under observation in October, 1920, with the following history. He was perfectly well until a year ago, when he had a cold, with cough and expectoration lasting a few weeks. The cold subsided, but a few weeks later he began to suffer with bedwetting, which has persisted ever since, and has recently grown worse. His condition was not improved, and several months ago he went to a prominent pediatricist, who advised that he be sent to a camp, but this did not relieve the bedwetting. About two months ago, in addition to the bedwetting, he began to suffer with intense supra-orbital headaches and attacks of dizziness and fainting spells, coming on in the daytime. These attacks have been considered by all the physicians who have seen him, including the prominent pediatricist, as a mild form of epilepsy. He is always constipated.

The patient was always a weak child. He began to walk at the age of a year and a half. The only disease he had in childhood was measles, though he has always been subject to colds, and had large tonsils and adenoids, which were removed. The patient is a Jewish boy, but it was not necessary for him to be circumcised, as he was born with a very small prepuce. He has always been backward at school. He is now in class 5 B, with all the children in his class of about the same age, but he is at the foot of the class.

He is very fond of meats, but not so fond of sugar.

His mother is alive and well, except that she suffers from severe attacks of migraine. She has four brothers and three sisters, every one of whom has attacks of migraine. His mater-

nal grandmother also suffered from attacks of migraine. His maternal grandfather died at the age of forty-five, probably of some cardiovascular disease. The patient himself has two brothers and three sisters, all younger, and well. Two older brothers died of cerebrospinal meningitis. His paternal grandparents lived to old age, the grandfather dying at the age of seventy-eight, his paternal grandmother is still alive at seventy-nine years of age and in such excellent health that she has survived the severe conditions in the war zone for the last six years and has come over to this country alone.

He is a rather thin boy, undersized, and somewhat stupid, apparently not sick. His lower jaw protrudes, but it is narrow, the superior maxillæ are narrow, his eyebrows are very heavy, the hair is unusually profuse, and there is a growth of hair joining both eyebrows. The skin is soft and rather smooth and delicate, and there is a very fine hairy growth on the dorsal surface of both forearms. The teeth have wide interdental spacing. The tonsils are absent. The uvula is split. There is an occasional pigment spot over the right clavicle and on both forearms.

Lungs and heart normal. Blood-pressure systolic, 100, diastolic, 80. The abdomen is negative.

He has a very small penis. No pubic hair. The testes are normal in size, but are undescended. He has a hypospadias.

The roentgenograph shows a very small sella turcica.

Basal metabolism —7 per cent.

This patient, who complains of nocturnal enuresis and of fainting attacks which are considered to be mild epileptic attacks, shows, as the only objective findings, signs of deficient development, namely, he is undersized, his mentality is below par, he has undescended testes, and has a rudimentary penis, a hypospadias, and a split uvula.

The undescended testes can be considered as a slight sign of genital deficiency, for normally the testes descend into the scrotum, and if there is an interference with the development of the testes there is also a limitation in its descent. Consequently, undescended testes are always undeveloped testes, and unde-

veloped testes indicate pituitary deficiency. Furthermore, the patient also has other pituitary stigmata, such as protuberant lower jaw, the bushy eyebrows, the increased interdental spacing, and the narrow superior maxillæ.

Incidentally, there are other signs of deficient development, the hypospadias, the split uvula, and the roentgenogram of the sella turcica corroborates the pituitary deficiency.

We therefore can conclude, on the basis of the objective findings, that the attacks of epilepsy and the nocturnal enuresis are merely symptoms of pituitary deficiency. The patient has been on intensive pituitary feeding for the last five months, with complete disappearance of the enuresis and marked improvement in the frequency and intensity of the "attacks," but he is still under treatment.

Case VII Epileptic Attacks with Pituitary Markings—J R, a boy of thirteen years, came under observation in February, 1920, with the following history. About six years ago, at the age of seven, he was suddenly taken ill with severe headache and fever. He was taken to one of the large hospitals in the city that night, and the same night he was operated upon for an abscess of the left kidney. Two weeks later the kidney was removed. He remained in the hospital for eight weeks, and he went home cured. When he came home he had a convulsion that lasted a few minutes. Since then he has had similar convulsions about every two to four weeks. At times he has dizzy attacks without actual convulsions. For the last two months he has had a convulsion about every day, and for the last week he has had convulsions a few hours apart. The attacks come on suddenly. He begins to complain of supra-orbital headache and then he has a convulsion. There are no aura. He has lost 5 pounds in weight during the last week. He has no temperature after the convulsions and he has no temperature between convulsions.

At the age of three he had scarlet fever, which was followed by otitis media and nephritis. He had measles the same year, and chickenpox a year later. At the age of six he had diphtheria.

"At birth he was not completely circumcised," and at the

age of two his mother noticed that the urine was coming from under the penis (hypospadias) He was operated upon for this condition, without benefit

He is very fond of sweets and meats His father is alive and well and has never been sick He has three brothers, all younger—ten, nine, and seven years of age respectively—all well His mother is perfectly well

The boy is a rather tall youngster, has very prominent supra-orbital ridges, he has rather bushy eyebrows, and there is an increase of hair between the eyebrows The nose is broad and prominent In the mouth the teeth are in good condition, and the interdental spacing is increased, the lower jaw protrudes somewhat forward

In the neck the thyroid is not enlarged The lungs and heart are normal The abdomen shows nothing of any pathologic interest The extremities are rather long, the fingers are long and broad The genitals are normal in shape and size, though not so large as usual, and there is a hypospadias The roentgenogram of the sella turcica shows a fairly normal sized sella, but an overlapping of the clinoids and occlusion of the roof of the sella

The patient came under observation on account of attacks of epilepsy which followed a nephrectomy for a purulent condition of the kidney just before the outset of the first attack The renal lesion was probably coincidental and of no etiologic value The only objective finding is that the boy has very definite acromegalic markings, with a hyospadias, and the roentgenogram shows a sella turcica which is occluded, although of normal size Consequently, it seems likely that the attacks of epilepsy have a relation with his evident pituitary markings He has been on pituitary feeding and has had only two mild attacks in the last eight months

CONTRIBUTION BY DR WILLIAM S McCANN

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THE LIMITATIONS OF METABOLISM DETERMINATIONS IN DIAGNOSIS

IN the discussion of the limitations of any laboratory test which is applied to diagnosis one has merely to consider the uncontrolled factors in the procedure. No one will disagree with the statement that a test is never better than its checks and controls.

The physician making a diagnosis is in the position of a judge trying a case, one of the chief functions of whom is to decide upon the admissibility of evidence. Having decided upon the reliability of the principal witness—the patient—he admits the history and then the evidence of his own five senses. The variations in reliability of these latter witnesses is generally recognized to be very great. Even to individuals in whom clinical perception has been most highly developed there remain certain fields in which evidence cannot be acquired by the senses unaided. For this reason we have steadily added to the list of instruments of precision and laboratory tests the function of which is to furnish evidence which is distorted as little as possible by human bias or prejudice or faulty perception. It behooves us then as physicians to inquire into the uncontrolled factors in our methods so that they may be properly evaluated.

In the procedure of determining the basal metabolism misinterpretations may arise from three sources—the apparatus and methods employed, failure to control conditions within

the patient, and the mind of the individual making use of the test

The apparatus used for metabolism determinations in clinical work is of four general types first, the respiration calorimeter, second, the respiration chamber, third, the open-circuit apparatus (Tissot's), fourth, the small closed-circuit respiration units. Of these four types the first, the respiration calorimeter, is the only one perfectly checked and controlled. In it heat production is determined simultaneously by both physical and chemical methods. In this it is unique. It shares with the second type the advantage of being capable of alcohol checks¹ and of measuring both the oxygen consumed and the carbon dioxide produced. In both of these types of apparatus it is possible to determine both heat and the products of combustion with great accuracy. However, both forms are expensive and bulky, and when operated, are time consuming. They will never be available for use in large numbers of cases. The first, which is the only one correctly called a calorimeter, has a decided advantage when it is desired to explore new and uncharted fields of metabolism, and in the establishment of normal standard values.

The third type of apparatus is exemplified by that of Tissot, in which a valve is used to separate the inspired from the expired air. The expired air is collected and measured in a spirometer and subsequently analyzed for oxygen and carbon dioxide. Its composition, when compared with that of the pure inspired air, enables one to calculate the amount of oxygen consumed and carbon dioxide produced. An excellent description of the technique of this procedure is given by Boothby and Sandiford.² The gas analysis may be done with great accuracy in duplicate. The principal weak point in the method lies in the possibility

¹ When a known weight of a chemically pure alcohol is burned in the apparatus a definitely known amount of heat is evolved, and from the chemical formula one may calculate just how much carbon dioxide is produced and how much oxygen absorbed. In the case of ethyl alcohol the ratio of the volume of carbon dioxide to the volume of oxygen is as 2 is to 3, in other words, the respiratory quotient is 0.666.

² Boothby and Sandiford. *Basal Metabolic Rate Determinations*, 1920, W. B. Saunders Company.

of undetected leaks, especially in the valves and mask, or around mouth-piece or nose-clips. These may be almost entirely avoided by care and skill. In general, the method has been found to give very satisfactory results, and in this clinic is preferred to the small closed-circuit methods.

Of this fourth type there are several forms, the most reliable of which is the old Benedict Universal Respiration Unit. This unit was not very portable, required large balances and almost as much time for its use as a respiration chamber.

Recently there have appeared several forms of apparatus designed chiefly for portability and rapidity of use. Of these, two are already in common use, both of which determine only the oxygen consumed, disregarding carbon dioxide completely. By this failure to determine carbon dioxide a gross error in technic may escape detection. For instance, the oxygen consumed by the patient is determined by the shrinkage in volume of a mixture of oxygen and air in a spirometer, or gas bag. It depends for its accuracy on complete absorption of the carbon dioxide given off by the patient. It has been the experience of all workers with closed-circuit apparatus that occasionally air finds channels through the absorbers and carbon dioxide escapes absorption. In this case the spirometer would give an apparently low reading for oxygen consumed and the metabolism would be reported lower than it actually was. If both carbon dioxide and oxygen had been determined the error, if large, would be detected by the finding of an abnormal respiratory quotient—that is, outside the limits of 0.72 and 1, which are the limits for all true combustion quotients with the single exception of a lower quotient sometimes found in severe diabetes. Indeed the finding of a quotient below 0.75 or above 0.90 may be regarded as highly suspicious, if the usual basal observation is being made sixteen to eighteen hours after food was last taken.

The disadvantages so far discussed may possibly soon be done away with by mechanical ingenuity and the training of physicians to standardize experimental conditions and to check their results. Far more subtle sources of error exist within the

patient The obvious ones are muscular movements, surreptitiously taken food, failure to rest for a sufficient time before the test, all of which may be avoided Mental excitement or agitation plays an important rôle with many patients in whom it may be readily overlooked This can best be illustrated by a case in point

Florence C , a young married woman aged twenty-one years, who entered the clinic complaining of severe headaches, was found to have a marked degree of vascular hypertension Albuminuria was present, but renal impairment if present had not reduced the phthalein excretion below normal nor increased the non-protein nitrogen or creatinin of the blood This patient was very emotional and neurotic Because of her nervousness, very prominent eyes, and occasional tremors a thyroid disorder was suspected In attempting to do the Goetsch test her fear of the hypodermic needle was sufficient to raise the blood-pressure 50 mm , so that no injection was made On the first day on which a metabolism test was attempted she remained motionless throughout the test, but her body was observed to be tense with excitement and apprehension The result of this test was found to be a variation of 49 per cent above the average normal metabolism Since the error was suspected the test was repeated on the following day On the second occasion the apprehension was allayed, the patient relaxed completely during the test The metabolism under these conditions was truly basal, and this time it was found to be only 11 per cent above the average normal

Such patients are not uncommon, but the difficulty is more frequently met with in patients with true hyperthyroidism in whom any unusual procedure is apt to produce an emotional reaction The nervous type of patient should always be subjected to a preliminary or "dummy" test as a matter of routine

Another type of difficulty deserves mention There are certain individuals who have the greatest difficulty in breathing normally through a mouth-piece, with a clip on the nose Even when a mask is used these patients will persistently overventilate

the lungs, either by increasing the rate of respiration or the depth, or both. This overventilation increases the oxygen consumption very slightly because of the increased muscular work, but it does increase the carbon dioxide excretion enormously. If carried to the extreme the elimination of carbon dioxide may occur more rapidly than the alkaline reserve of the blood is reduced, so that the alkalinity of the blood may be increased and even tetany has been produced by Grant and Goldman.¹ Such extremes of overventilation would hardly be obtained in a metabolism determination, but the process involved is the same. The increased carbon dioxide output is not due to increased oxidation, and the respiratory quotient would be found to be too high. It seems important to go into this matter at length to illustrate the pitfalls in the way of determining the metabolism from the carbon dioxide alone as has been recently suggested. It should be borne in mind, therefore, that any method of measuring the heat production which depends on determination of only one of the gases exchanged is untrustworthy and should be used with great caution and reserve in interpretation of results.

It is in interpretation that we are most limited, because we are still in ignorance of some of the intrinsic processes of metabolism and of the various factors which control them. Thyroid disorders have stood out in the minds of physicians as the diseases of metabolism par excellence. The correlation of the findings of calorimetry with the demonstrable lesions of the thyroid gland has progressed to a satisfactory degree. However, lesions of the thyroid are not the only ones which lead to marked quantitative changes in the metabolism. In the anemias, in leukemias, and in certain of the rare diseases, not to mention the fevers, the metabolism may be greatly increased without any demonstrable thyroid disorder. Diagnosis must depend on other things than a metabolism test. A report of a high or low basal metabolism has just the same kind of significance as a high or a low leukocyte count. Both may be

¹ Grant, Samuel B., and Goldman, Alfred. A Study of Forced Respiration. Experimental Production of Tetany, *Amer Jour Physiol*, 1920, III, 209.

admitted as contributory evidence, in a differential diagnosis, provided one is sure that they were done accurately

It should be pointed out that before metabolic disorders in childhood can be successfully investigated it will be necessary to establish normal standards from a study of a larger number of children of each age and weight and height

Even in adult life there are certain periods in which the number of normal cases so far studied has been too few This is especially true of the menopause in women Inasmuch as so many abnormal processes frequently arise in the climacteric it will be very difficult, in the establishment of normal standards, to eliminate all but studies of normal women undergoing the normal menopause

It is to be remembered also that there is a normal range for variation in the basal metabolism, just as there is for normal body temperature This range is from 10 per cent above to 10 per cent below the average normal value For clinical interpretation of results obtained with the portable forms of apparatus it would seem advisable to extend the normal zone from minus 15 per cent to plus 15 per cent

The old humoral pathology has had a modern revival in endocrinology, a field which has been entered to a large extent by those who prefer indulgence in luxurious speculation to laborious scientific observation Many fantastic theories of so-called *dysfunction* of ductless glands are current, in the diagnosis of which absolutely no support has been lent by accurate basal metabolism studies Among the reliable investigations which have been made one finds evidence that the basal metabolism is increased or decreased with certain types of thyroid or pituitary disorders These changes in metabolism have been so far purely quantitative There is no evidence of a qualitative change which would support the theories of an abnormal secretion elaborated by these glands

Of the value of metabolism tests in measuring the severity of thyroid disease there can be no doubt No better way has been devised for the purely objective determination of the effect of treatment But the limitations of calorimetry as a means of

diagnosis must be recognized before the literature becomes flooded with a mass of inaccurate data and conclusions

It is not to be understood that any plea is being made against calorimetry. On the contrary, it is anticipated that calorimetry will contribute enormously in practical results to the physician not alone in diagnosis but also in improved dietetics which will result from a careful study of the food requirements and of the nature of the oxidations in disease

CLINIC OF DR HAROLD E B PARDEE

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DISEASE OF THE CORONARY ARTERIES

One of the Chief Causes of Angina Pectoris, Importance of Differentiating the Various Causes of Precordial Pain, Common but Atypical Manifestations of Coronary Disease Typical Cases and Full Discussion of Management and Treatment

I WANT to consider with you today the symptoms and physical signs which may result from an obstruction to the blood flow in one of the branches of the coronary arteries such as is brought about by arteriosclerotic narrowing This will immediately suggest to you, I am sure, the attacks which are called angina pectoris, and it is right that it should do so, for coronary artery disease is one of the chief causes of angina pectoris It shares this distinction, however, with disease of the aortic arch, and with several other less frequent causes, such as valvular disease, pericarditis, myocardial disease, and tobacco-poisoning

Coronary disease can give rise to pain in one of two ways Either there is a sudden stoppage of the blood flow in one of the branches of the artery due to thrombosis of the vessel, very rarely to an embolism, or there is a reduction of the blood flow due to an arteriosclerotic narrowing, so that the demands of exercise for an increased coronary flow cannot be met. Let me emphasize that it is not necessary that a patient who has disease of the coronary arteries should also have demonstrable arteriosclerosis elsewhere, though I believe that well over half of the patients will show it Recently Dr Herrick, of Chicago, has reported a series of 3 cases of coronary artery thrombosis with autopsies, and in only 1 of these was more than minimal arterial disease found outside of the coronaries

Attacks of angina pectoris constitute a very definite clinical picture, with which you are no doubt quite familiar. Typically, there is a sudden severe pain situated behind the lower sternum, radiating perhaps to the neck or left shoulder or to the inner side of the left arm, associated with a strong sense of constriction of the chest, so that the breath is caught with difficulty, and with a sense of great weakness and anxiety, so that the patient feels that he will surely die. At the time of such an attack the patient is prostrated. The pulse may or may not be increased in rate, but is often irregular. There is usually a hyperalgesia of some area of the skin of the left chest anteriorly, and this hyperalgesia may extend down the inner side of the left arm, usually persisting for several hours after the attack. These attacks are very typical and are not difficult to recognize, either when they are seen or when the patient tells you about them, and I believe that to such attacks as these the term *angina pectoris* should be confined.

By keeping the name for these typical attacks you will deprive yourselves of a convenient scrap-basket into which you are apt to throw any atypical pains occurring in the region of the heart or in the left anterior chest, and will tend to become more particular in the diagnosis. The terms "angina minor," "angina sine dolore," "false angina," "angina abdominalis" have been coined by writers who wished to include with angina pectoris certain atypical symptom groups which they believed to have the same cause as angina pectoris. It may be that they are right, in part at least, but it is certainly true that by abolishing these terms and speaking of the symptoms as "a pain or a discomfort in such and such a situation," you will greatly stimulate your desire for a correct anatomic diagnosis. You will be much more liable to consider carefully each of the possible causes of such an abnormal sensation than if you use such pseudodiagnostic terms as "mock angina" or "angina abdominalis." I believe it would be a very excellent thing for our understanding of the condition if angina pectoris itself were thus dismembered, and spoken of as the pain caused by aortitis, or by coronary disease, or by myocardial degeneration, or by tobacco-

poisoning, as the case may be, but I am afraid that this project is too idealistic to be achieved for some time at least

Besides being a common cause of angina pectoris, coronary artery disease may lead to a chain of symptoms in which the prominent features are quite different from those of the typical attacks, and it is to these less outstanding but really much more common manifestations that I want to draw your special attention

You will find the clinical evidences of coronary disease are usually very insidious in their onset, and very often are considered by both patient and physician to be due to the stomach. The following patient will serve as an example of this mode of onset. He is a man forty-five years of age, and has been troubled for three or four years by a sense of fulness and discomfort in the epigastrium whenever he ate a large meal. He never felt nauseated and never vomited and was not constipated. Also, and this is important for the diagnosis, if he had occasion to walk for a distance of over 100 feet just after a meal he would have a sense of pressure, as he said, "in the stomach," but when asked to point out the situation of the feeling it was found to be behind the lower 2 or 3 inches of the sternum. At irregular intervals of from two to four months he would have attacks quite independent of meals and usually when he was sitting quietly, which consisted of a sense of heavy pressure "in the pit of the stomach," which again turned out to be behind the sternum, accompanied by a feeling of great weakness and a sense of difficulty in getting the breath. These attacks would last from ten to thirty minutes, during which time he would repeatedly belch up air, always with temporary relief to the pressure sensation and to the sense of dyspnea. This patient took very little exercise, but the ordinary exertions of walking and climbing stairs never caused him any shortness of breath, nor any precordial pain or discomfort except as mentioned when he would walk just after a meal.

During the last year the attacks of epigastric pressure have increased in severity, and the sensation has at times amounted to a pun, referred to the lower sternum and described as a

"tightening up" The sense of weakness during the attack and the feeling of difficulty in breathing have also increased

One day while standing at a window he suddenly had a severe attack of pain under the lower sternum, passing through into the back He felt suffocated and that he could not get his breath, and he fell to the ground unconscious After ten or fifteen minutes he regained consciousness, and then was found to have a soft, small irregular pulse at the rate of 54 per minute, which later came to be regular at about 42 per minute

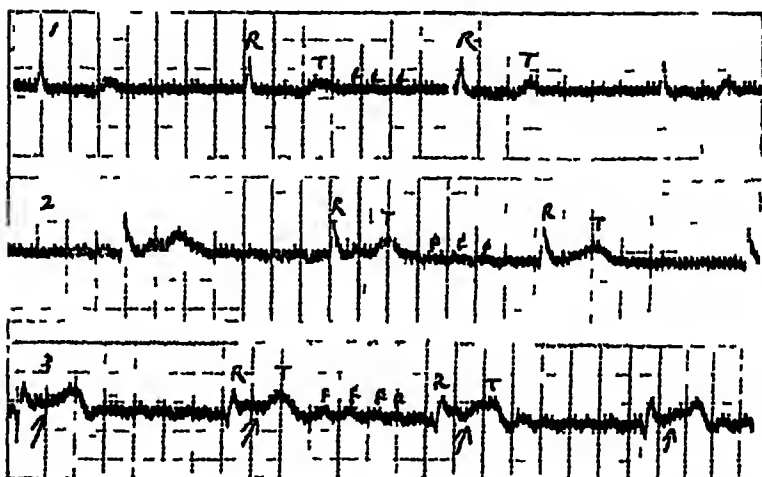


Fig 160—Electrocardiogram taken just after an attack of coronary artery occlusion The characteristic feature is the high level at the point in the ventricular complex between the R and T waves which is indicated by the arrows This patient shows this feature in Lead 3 The time marker of these records indicates one-fifth second by the space between each fifth vertical line, which line is seen to be slightly accentuated

At this time he was without apparent dyspnea and appeared rather pale The heart was not enlarged, the sounds at the apex and base were weak, snapping, and distant, there were no murmurs His blood-pressure was 90 mm systolic and 60 mm diastolic, a very significant feature, the radial arteries were moderately thickened, and there was an area of hyperalgesia about 2 cm in diameter over the inner part of the fourth left intercostal

space Examination of the lungs and abdomen showed nothing of significance The electrocardiogram which I show you (Fig 160), taken about eight hours after the attack, indicates by the wavelets marked f, f, f, that auricular fibrillation was present, and the peculiar T wave is of the form that we have come to associate with a recent occlusion of a branch of a coronary artery, the interval between the Q, R, S group and the peak marked T being raised above the base line



Fig 161—Electrocardiogram of the same patient taken several days after the attack The characteristic feature is the sharply downward curve of the T wave which is seen in this record in Lead 3 at the point indicated This feature has been found to persist for many months after the attack

The patient made a rather rapid recovery and was able to be up and about again in a week He now, however, complained of substernal pain on walking, which after several hundred feet would make him stop to rest until it had passed off His electrocardiogram gradually changed to the curve of Fig 161, which still shows auricular fibrillation, with a more rapid ventricular rate, and which shows the sharply downward curve of the T wave that we have come to associate with the scar of an old stoppage of a branch of a coronary artery He now

presents a quite typical instance of pain due to insufficient coronary flow, having had a rather atypical attack of coronary occlusion

This patient affords a very good example of how the symptoms from the heart may be continually referred to an adjacent organ. It is very easy for one to fall into this error in the cases with a gradual onset, which do not at first have sharp pain or striking symptoms on exertion, to direct our attention to the heart. The *confusing features* which tend to focus your attention upon another organ than the heart are that the pain may fail to show the typical situation or character, and that with the attack there may occur reflex disturbances in other organs, as the belching of gas in this case and the nausea, perhaps with vomiting, that may occur in other cases. Sometimes even a polyuria may appear during or at the end of an attack, and as the pain in these cases radiates more downward and to the right, you may be misled into thinking the affair a Dietl's crisis due to floating kidney.

There are though, in a careful history, certain *features by which you should recognize* these cases. The symptoms develop at the earliest after the age of thirty-eight or forty years. They tend to appear first after a full meal, or after exercise, or when exercising after a meal. There is a sense of suffocation or difficulty in getting the breath during the attacks, but as this history is usually not volunteered by the patient, it must be obtained by guarded questioning. Note that in spite of this sensation of suffocation there is no objective dyspnea. The situation of the pain or discomfort if pointed out by the patient will be found to lie at the lower part of the sternum, and not, as he describes it, "in the stomach."

The gradual and insidious onset that I have outlined is, of course, but one of the ways, though a very common one, by which coronary artery disease will make itself known. Sometimes it may be very frank in its manifestations, with pain on exertion and occasional attacks of sharp pain when at rest. In some patients the diagnosis may be revealed, even though the pain is not severe, or typical by the peculiar anxiety and dread

or "sense of impending death" which is sometimes present with the attacks

In yet other patients the disease will flash out very abruptly. A person who has always considered himself in the best of health and in whom even the closest questioning will fail to reveal any symptoms of disease may suddenly have an attack of the greatest severity. These sudden severe onsets are very often not recognized as due to the heart, because of the frequently atypical character of the pain and because of the nausea and vomiting which practically always accompanies them. The pain in these severe attacks may sometimes, curiously enough, be but slight, or it may mislead us by radiation to the epigastrium or to the region of the liver or through to the right lumbar region or to the right shoulder-blade. These attacks are very apt to be considered due to an acute condition in the abdomen, perhaps an acute gastric derangement of one sort or another, perhaps a cholecystitis or gall-stone colic and occasionally even to a renal calculus or a kinked ureter due to movable kidney. Occasionally a pleurisy will be suggested, especially if the pain radiates to the right and the dyspnea is more evident than usual.

I have seen a patient whose first symptoms were apparently typical of "acute gastric indigestion." There was severe pain referred to the epigastrium, with nausea and vomiting, and marked prostration. The heart and pulse seemed undisturbed, though the blood-pressure was not measured. The patient was able to get up about two hours after this attack and seemed well enough, though weak. He was allowed to go to the lavatory, where he was found dead a few moments later, and the autopsy showed a thrombosed coronary artery. It is not usual though for the first severe attack to be thus fatal. The first attack is usually survived.

How then are we to recognize the results of coronary disease, and differentiate them from the many other conditions with which they may be confused? It is not, of course, possible for you to do this in every case the first time you see the patient, but by careful attention to certain details I feel sure that we

can raise the percentage of correct diagnoses, and that certain of the lamentably common mistakes will be easily avoided

Consider especially the pain and the physical signs which will be considered later The pain is a midline pain Its characteristic seat is behind the lower sternum opposite the third and fourth intercostal spaces, and at the xiphoid or in the epigastrium opposite the fifth intercostal space Rarely it is felt as high as the second intercostal space When severe, it radiates and passes laterally to the left or right at these levels, and may seem to pass through to the back, or if felt in the higher levels it may pass out into the ulnar aspect of the arm and forearm, and rarely to the neck Rarely pain starts laterally and, becoming more severe, radiates to the central position In its lesser manifestations there may be no pain at all, but merely a sense of discomfort, felt especially under the lower sternum or in the epigastrium, and not, as the patient will say, "in the stomach" It is never a constant sensation, but comes in *attacks*, and these attacks either arise spontaneously when the patient is at rest or come on as the result of exercise, so that the patient must stop and rest until the discomfort passes off It has a very peculiar character best described as a gripping or a sense of compression beneath the sternum

The attacks are not accompanied by objective dyspnea at the time, though this may appear shortly after the very severe ones, when cardiac failure with pulmonary congestion has set in The patient may have a sense of suffocation or of precordial oppression during the pain, but this passes off quickly and does not lead to labored breathing in ordinary cases It will not usually be mentioned by the patient unless inquired for, as it is not a noticeable symptom This is a very important and distinctive feature about coronary occlusion which separates it from attacks of uremic or cardiac dyspnea and from pulmonary embolism, in all of which shortness of breath, both subjective and objective, is a prominent feature

The pain of coronary occlusion is continually being confused with the pain due to other conditions in the chest and in the upper abdomen I shall have to take these up serially with

you and consider how you should be able to recognize in each case the true cause of the disturbance. Each time a patient suggests to you one of these diagnoses, you should think "Is this group of symptoms perhaps due to the coronary arteries?" If you do this your mistakes will be fewer.

The pains produced by the *aortitis* of syphilis, rheumatic fever or influenza, and by increased arterial pressure are very difficult to distinguish from the pain due to coronary disease, in fact, so great an authority as Sir Clifford Allbutt has attributed almost all pains of this character to aortic or hypertensive disease, allotting to the coronaries a very small part in their production. It seems possible, though, to separate a group of patients from among those complaining of pains of this sort whose symptoms are more suggestive of disease of the aorta than of the coronaries. Their pain is situated higher under the sternum, opposite the first and second intercostal spaces. It has a greater tendency to radiate down the arm and especially into the neck which the pain of coronary disease seldom does, and besides this, it has little or no tendency to occur at night or when the patient is at rest.

When aortic disease has progressed to the formation of an aneurysm there may be pains in the chest of one sort or another, but they are only rarely of a type to be confused with the pain of coronary disease. They have a more constant, less paroxysmal character and have not usually the typical situation and radiation. Moreover, by use of the fluoroscope any aneurysm large enough to cause pressure-pains will be readily seen, and the lesser dilatation of the aortic coats which precedes aneurysm formation can also be made out. You should never omit a fluoroscopic examination when attempting the diagnosis of any pain of the sort we are discussing, for it enables us to examine the aorta itself. True, there are degrees of atheroma that are confined to the intima of the vessel and others which may invade the whole wall but have not yet given rise to a weakening or dilatation. A negative examination cannot, therefore, exclude the presence of aortic disease, but very often the fluoroscope will reveal a local dilatation of the aorta or a lengthening

of the arch with increased tortuosity which cannot be demonstrated in any other way. Because we can turn the patient while he is under examination and thus obtain oblique views of the aorta, the fluoroscopic method is far superior to the x-ray photograph.

The pain we are considering may be confused with the pain of *neuritis of an intercostal nerve*, but you can distinguish them by the fact that neuritis pains tend to be more continuous, and are aggravated by movements of the trunk. There will also with neuritis be a tenderness over the course of the nerves right around the thorax on the affected side.

Rarely you will be uncertain whether you are dealing with the onset of an *acute pleurisy* or with a sharp attack of coronary pain. These can usually be distinguished by the character of the respiratory embarrassment. With anginal pain there may be a sense of dyspnea, but the respiratory movements are not rapid and never have the catchy embarrassment which is so typical of pleurisy.

Pain over the heart occurring in patients who have *myocardial disease* or *valvular disease* with signs of cardiac failure, or with *pericarditis* or with *paroxysmal attacks* of tachycardia or auricular flutter or auricular fibrillation is another source of confusion. I imply a distinction between a patient who has coronary pain associated with any of these conditions and one who has a pain that is due in some way to these conditions themselves. This cardiac pain is of a different character from that of coronary origin, being mostly to the left of the midline, and radiating to the region of the apex-beat, or being felt only at the apex. It does not have the radiation to the back, neck, or arm except when very severe, and is a more continued pain than the gripping paroxysmal pain of coronary disease. Its character is more aching, even though it should be, as it sometimes is, very severe indeed. When these conditions cause pain there is nearly always objective dyspnea, a very rare occurrence with coronary artery attacks, as has been stated.

The pain about the heart felt by *neurotic patients* whose attention has been focused upon the heart, the effort syndrome

or neurocirculatory asthenia cases, may in some respects simulate coronary artery pain, as may also the pain felt by patients with *hyperthyroidism*. It is not in either case a midline pain but lies to the left of the sternum like the pain of cardiac disease and is most often situated about the region of the apex-beat. That these patients have typical areas of hyperalgesia may lead you to a stronger belief that organic disease is present, but you must not be deceived by this into a diagnosis of cardiac disease. These pains like those of coronary disease may be brought on or increased by exertion, but there is an irregularity of occurrence after exercise which is characteristic, and this, taken with the lateral situation of the pain, and the evidence of a neurotic make-up of the patient should enable us to readily recognize the origin of the symptoms. It is important to remember that these pains do not occur with the milder forms of hyperthyroidism so that the rapid pulse or tremor or some of the other signs or symptoms of Graves' disease will be present to help you.

The overuse of *tobacco* can cause pains which are quite typical, and which are almost indistinguishable from the pains under consideration. They will cease however in from three to six weeks after stopping the tobacco so that our doubt will not be for long. It is difficult for me to understand why some should have this effect from tobacco while others are quite free from it when using an equal or greater amount and it is not at all inconceivable that tobacco produces this pain by acting upon an already formed basis of disease which is not sufficiently marked to produce symptoms by itself alone. I have this impression but have not yet been able to follow patients sufficiently long after their "tobacco angina" has ceased to decide whether or not they are destined to develop the real disease.

The *abdominal conditions* which are from time to time confused with severe attacks of coronary occlusion may or may not constitute a difficult diagnosis. *Gall-stone colic* *acute cholecystitis* the *perforation of a gastric ulcer* and more rarely the symptom-complex of *Dick's crisis* will often present themselves as alternative diagnoses with coronary pain. They should be

distinguished from coronary disease by a careful search for the special signs of each condition. The jaundice or the distended gall-bladder and the low situation of the pain, below the xiphoid and more to the right side, the presence of a tender point or hyperalgesia over the gall-bladder region, these are the diagnostic points in the gall-stone or gall-bladder conditions. The perforation of a gastric ulcer into the lesser peritoneal sac is most difficult to diagnose from certain severe attacks of coronary occlusion. The prostration may be equally marked in the two cases, and the pain of such a perforation is not so severe and striking as if the perforation had been toward the front, while abdominal rigidity and tenderness may be absent for a time at least. The chief feature by which they may be distinguished is the heart action. The coronary disease does not lead to such rapidity of the heart and the gastric disease does not lead to irregularity. Within a few hours after a perforation a leukocytosis will have developed, and also a more typical pain, but by this time the course of the patient's symptoms will have made it clear which of the conditions is present.

Most difficult of all is the distinction between the lesser symptoms of coronary disease and the *chronic gastric indigestion* which may arise from *chronic gastritis* or *perigastric adhesions*, or as a *reflex from gall-bladder disease* or *chronic appendicitis*. The first case presented to you today was an instance of this sort, and shows how little suggestion of cardiac disease may sometimes be apparent. The distinguishing feature of the coronary condition is the fact that the pain or discomfort is increased by exertion, and if, besides this, there should be occasional spontaneous attacks while the patient is at rest, then the evidence for a coronary origin is very good.

The physical signs of coronary disease are lamentably few. Even if the patient is examined directly after an attack there may be nothing found to lead to a suspicion of cardiac disease. The heart sounds are usually faint and the first sound at the apex more valvular than normal, but there is not sufficient change to lead to a definite diagnosis of abnormality, nor is the heart enlarged except in severe cases when heart failure sets in.

There are, however, five positive findings which may appear upon examination of the patient. They are just as likely to be present after mild attacks as after severe ones, and should be carefully searched for.

1 An area of hyperalgesia may be found in the area of distribution of the pain, so that the skin is abnormally sensitive to pressure or to pinching.

2 The heart may show the irregularity of premature beats, or of auricular fibrillation or heart-block. This would amount to a positive finding only if these irregularities were not previously present in this patient.

3 The systolic blood-pressure and especially the pulse pressure are found to be abnormally low during the attack. These increase as the patient recovers and will remain depressed for a longer time after the more severe attacks.

4 A pericardial friction-rub may be heard, perhaps only over a very small area and perhaps for only a very short time. This develops, if at all, at some time during the first twenty-four hours after the occlusion, and is due to an area of fibrinous pericarditis over the infarct.

5 The characteristic electrocardiogram may be obtained.

The finding of any of these things should make you strongly suspect the presence of coronary disease, and when taken in connection with the fact that the patient has attacks of discomfort in the region of the heart should be considered very good evidence. The last two of these findings should be considered pathodermomic.

The electrocardiographic record is a recently recognized sign of occlusion of the coronary arteries. The change in the T wave which I have pointed out to you in Fig 161 occurs in a large proportion of patients who have these symptoms of disease of the coronary arteries, in well over two-thirds of all. It denotes an area of infarction in the ventricular wall, and shows that a coronary branch has been stopped by a thrombus at some previous time. It is, therefore, a matter of great importance to the patient to have such an electrocardiogram, for it indicates that the ventricular muscle is scarred, and that the

scene is set for a further thrombosis. On the other hand, it does not contraindicate a certain amount of physical activity, for I know of one old gentleman who has played 18 holes of golf quite regularly for well over a year since this abnormal electrocardiogram was found. He finds, though, that he must play on courses which are not hilly, on account of the pain that is brought on by attempting an ascent.

Treatment—Now a word as to the treatment of this condition. It falls into two main categories—that directed to the relief of the attack itself, and that directed to lessening the occurrence of the attacks and the progress of the causative arterial disease.

During an attack the patient must remain quiet. This is the more imperative in the severer attacks, for an extra burden on the heart due to any effort might result in fibrillation of the ventricles with sudden death. This was probably the cause of death in one of the cases mentioned today. It is usually not difficult to keep the patient quiet at first, for the nature of the attack is such that he often feels that he does not dare to move. After this severity has passed off, however, he must still remain as quiet as possible, and after a bad attack should be in bed for a week at the least, no matter how well he may appear to feel.

To relieve the pain or discomfort of an attack which is brought on by exertion it will often be sufficient to stop the exertion, and this may be aided by the use of nitroglycerin, $\frac{1}{10}$ grain dissolved in the mouth. With nitroglycerin it will often be possible to ward off an attack which the patient feels is setting in. A larger dose than this will not be necessary at first, but may come to be so after a toleration for the drug has been established. If we start with large doses the unpleasant symptoms of throbbing and fulness of the head may be very objectionable. Used in this way, nitroglycerin acts in somewhat less than five minutes, but if a quicker action is desired it may be obtained by the inhalation of amyl nitrite from a handkerchief in which one of the glass pearls has been crushed. Again, the patient should inhale not too strongly at first, in order to avoid the throbbing head of overdosage.

When a patient is found to be suffering greatly from the pain and when the nitrite drugs do not relieve this there is every reason for giving morphin hypodermically. The dose should be $\frac{1}{2}$ grain and with it $\frac{1}{2}$ grain of atropin sulphate to do away with whatever increased vagus inhibitory effect upon the heart might be caused by the morphin. Papaverin has been shown to have a very marked vasodilating effect upon the coronary arteries. This might be a very helpful action when a large branch is stopped by a thrombus, for it would increase the blood flow to the anemic area by affording a wider bed of collateral anastomoses. It is a new drug and I have not seen it used.

Theobromin too is said to have this action of dilating the coronary arteries and should be used after an attack in 15-grain doses three times daily. It is obviously a very difficult thing to decide whether a drug helps in recovery from such attacks as these but since it has this dilating action upon the coronaries it should also be of value in warding off attacks and in increasing the ability of the heart to function without pain. Forscheimer has recommended it for this use and it appears to have benefited most of the patients whom I have seen use it.

The most important feature of the interval treatment is that the patient should never subject himself to an exertion or to a mental strain or excitement which he has found is able or even liable to cause an attack. Each attack of pain after exertion or excitement seems to make the next one come easier. If it is necessary for the patient to remain in bed for a time to achieve this object then he should do so but if bed is not thus indicated I do not feel that it is necessary or even advisable. A certain amount of exercise and especially out-of-doors exercise is very desirable for these patients if they can take it without approaching the degree of exercise which tends to precipitate an attack. The same qualification should decide the advisability of continuing at their occupation. Often after a rest period of two or three or four months a man can return to his occupation without a return of the attacks and without apparent harm coming from it.



CLINIC OF DR REUBEN OTTENBERG

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PRACTICAL ASPECTS OF BLOOD TRANSFUSION

In spite of the vast amount that has been written and said about blood transfusion in the last ten years those who are actively in contact with this subject are constantly surprised at the number of important details connected with transfusion concerning which the average practitioner is not accurately informed. Furthermore on account of this lack of familiarity, the practitioner is afraid of and often hesitates to employ transfusion in suitable cases. The result is that this valuable therapeutic measure is not used nearly so frequently as it easily could and should be. The contact of the average physician with actual blood transfusion usually commences when a transfusion is suggested for his patient by some consultant. In these cases often the transfusion is suggested as a desperate measure for a patient already in a very serious condition.

Transfusion should not necessarily be regarded as a "last ditch" emergency measure. In most instances it should be performed much earlier in the course of the disease than it is. For this reason, I have chosen for discussion certain simple questions that arise in connection with transfusion.

After a transfusion has been suggested the practitioner usually calls in some specialist and proceeds to ask him questions. These inquiries which come up again and again evidently represent points which the man who has never actually performed or witnessed a transfusion wishes to know, and I think I can proceed to illuminate the subject best by answering them.

The first question is almost invariably "Is transfusion dangerous?"

The answer is "It used to be, it is not now."

Indeed, the traditions of accidents following transfusion still lurking in the mind of the public are what make people turn to transfusion with doubt and hesitation. Since the days of Harvey there have been three or four historic periods during which transfusion has been introduced and actively practised for a short time, only to be given up each time because of the numerous accidents reported. Today, however, the operation is safe, and it has been made so by a better understanding of the blood incompatibilities which were the cause of most of the accidents in the earlier periods of transfusion history. This better understanding dates back chiefly to the discovery by Landsteiner, of Vienna, in 1901 of the agglutinating property which the blood-serum of certain individuals has upon the red blood-cells of certain others, and by the discovery by Maragliano in 1897 of the hemolytic or dissolving effect which the serum of certain individuals has upon the cells of certain others.

It is not my purpose at present to go into the extraordinarily interesting details of these blood differences and the tests that are made to detect them. Suffice it to say with regard to both hemolysis and agglutination that all human beings fall into four definite, permanent (for the individual), and hereditary groups that transfusion between two individuals of the same group is safe, that transfusion between two individuals of different groups may be safe under certain conditions—for which the practitioner had best depend on the laboratory man who makes the tests. The essential point is that the physician should feel that if the tests are satisfactory the operation will be safe.

The next question is "How shall I have the tests made?"

The method is very simple. It is necessary to draw only about 5 drops of blood from a prick of the finger, collect them in 1 or 2 c c of a 3 per cent sodium citrate solution, or, if that is not at hand, in a like quantity of normal salt solution, and send the specimen to the laboratory.

All well-equipped laboratories, at least in the larger cities, are prepared to make these so-called grouping tests for transfusion, and can report back an answer to the medical man in fifteen to thirty minutes from the time the blood is received.

"Can accidents happen if the tests are satisfactory?"

They can, but they are extremely rare

Personally, I know of 3 such cases. One was due to a misunderstanding about the donor's group. The patient showed all the symptoms of acute hemolysis when about 150 c c of blood had run into his veins, but he recovered. The other 2 cases were fatal and were unexplained. One was an acute death, in an already almost moribund case of postpartum infection, the other was a case of phlebitis, and the symptoms were those of pulmonary embolism. Besides these, Lindeman has reported 3 unexplained accidents in cases in which the tests were performed, two of which, however, were actually due to mistakes in the tests. These instances which I mention are, of course, important, but they are very few in comparison with the many thousands of transfusions which have been made.

"Suppose the case is so urgent that there is no time to make any tests, what then, is the risk if one goes ahead and does a transfusion, selecting any available person as blood donor?"

The answer is "Go ahead." In a desperate case, the danger to the patient from acute anemia, or whatever the other indication for transfusion, is greater than the percentage of risk from transfusion accident.

Thus Crile, in 100 cases of transfusions made without tests, reported 2 deaths, and Bernheim collected 800 cases without tests, in 16 of which hemolysis occurred—fatal in 4 instances. Karsener has calculated from a study of the groupings that in over 40 per cent of the cases if one does transfusion at random without tests there is no danger whatever, and in 1909 I published an explanation of certain safety factors which minimize the danger when incompatible transfusions are made. I showed then that the danger of such incompatible transfusions is always greater if the patient's blood-serum has agglutinative or hemolytic properties toward the blood-cells of the donor than if the reverse is true, and that on account of the quantitative relationships the danger is minimal in those cases in which the donor's serum has these injurious effects on the red cells of the patient. In actual practice this has proved to be true and today it is

generally conceded that where one cannot find a donor of the same group as the patient, one should select a donor of a group whose red cells are not injured by the patient's serum. Under these conditions transfusion is safe. Since there is one group (Landsteiner's Group I) whose red cells are not affected by any human serum, this group has come to be known as the "universal donor" group, and in the practice of transfusion during the late war individuals belonging to this group were kept, or their blood was held ready at the casualty stations for emergency use.

Besides the factor of safety inherent in the quantitative relationships, Moss has pointed out that there exists in many normal individual's plasma an "antihemolysin," which interferes with hemolysis in the body to a certain extent and is undoubtedly an additional safety factor.

While the danger of accidents undoubtedly does exist (and indeed, if one does a large series of transfusions without selecting donors by tests one is absolutely sure to have accidents), nevertheless, when up against a case where the patient's life is in jeopardy and immediate transfusion may save him, one should consider the relatively slight risk of transfusion accident as outbalanced, and should go ahead.

There is another danger, referred to by Dr. Libman and myself in one of our publications, namely, the danger of suppression of the urine, and in our expression of opinion, we brought up the question whether in the instance referred to the suppression (from which, however, the patient recovered) was due to sodium citrate. Since then Goormaghtigh has published a similar case, in which, however, the suppression followed a transfusion by the syringe method, no citrate of soda being used. The possibility, therefore, of the occurrence of such an accident in an individual with already badly damaged kidneys must be considered, though the accident is an exceedingly rare one. In fact, I have seen a large number of transfusions on individuals with diseased kidneys, and several on individuals with only one kidney, none of which showed any untoward effects.

The next question that usually comes up is, how to find a donor

In many instances this is readily settled, for relatives and friends step forward and volunteer their services. In such cases there is nothing to do but to test the blood of as many of them as possible for compatibility. If one wishes to use a near relative as donor and the transfusion has to be done at once, it is usually sufficient to interview the would-be donor privately as to possible syphilitic infection and to look him over physically. In the case of all other donors a Wassermann reaction should be done before the transfusion is made. Common sense, of course, suggests the natural exception to this, namely, in extremely urgent cases in these cases, if one were to put oneself in the patient's place, one would calculate on preferring the relatively small risk of transmitted syphilis as compared to the relatively great risk of omitting the transfusion.

When donors cannot be obtained from volunteers among the patient's friends and relatives, it is always possible (in large centers at least) to obtain the so-called professional donors by advertisement or from lists of such donors, already tested, available in almost all large laboratories and hospitals. In fact, in emergency work it is usually best to depend on such donors for the Wassermann test and blood group test have already been made.

When the donor is a member of the family, the donor always asks "Is there any danger to me?"

The answer can be unhesitatingly given "No."

In many thousands of transfusions now on record there has never been any serious harm done to a single donor.

Another question always asked is "How much blood will be taken?"

The answer should be "Not enough to do any harm."

Usually it is better not to tell the donor the exact amount to be taken because it always sounds larger to him than it really is. In practice 500 to 1000 c.c. is the usual transfusion amount (a pint to a quart). The donor can furthermore be assured (provided of course that he is physically fit) that he

can easily stand the loss of blood, that he can return to his work the following day, and (if he is a professional donor) that he will be able to again act as donor in about three months

The donor, and the family as well, want to know whether the transfusion is painful

The answer can be "Practically, no"

Hypodermic infiltration of the skin and subcutaneous tissues with novocain ought to be done before the cannula is inserted into the vein in all except the most urgent emergency cases, and in the vast majority of cases it is not necessary to make any incision through the skin, the cannula simply being pushed through the skin into the vein

Another question that is always asked is "How much blood will you transfuse?"

This really resolves itself into several questions

(1) How much can the donor give?

If he is a full-sized man weighing 150 pounds or more, one need not worry about this question, but can safely draw 1000 to 1200 c c from him if necessary. If he is of smaller stature or there is some doubt about his physical fitness, or if the donor is a woman, it is generally safest not to exceed 500 to 600 c c, getting blood from two donors if necessary

(2) How much blood does the patient need?

This will vary, of course, according to the patient's size and the disease from which he is suffering. In acute hemorrhage it is not necessary to give as much as the patient has probably lost. Generally in adults one gives 500 to 1000 c c, and the effect in resuscitating the patient is often brilliant. With children proportionately smaller amounts are required, and with infants usually about 100 c c. In chronic anemias it is desirable, of course, to raise the patient's hemoglobin percentage as much as possible. On the other hand, one has to remember that just in these chronic anemias it is impossible to transfuse huge amounts of blood at one time because the patient's blood volume, as a rule, is not decreased, and in some of the chronic anemias it is actually increased, the quality and not the quantity being at fault

The question then comes up "How much rise in the percentage of hemoglobin can be expected from a given transfusion?"

In a publication issued in 1914 Dr Libman and I showed how this can easily be calculated beforehand. Suppose that we are dealing with a patient who weighs 150 pounds. Let us assume that the average figure for the blood volume is, roughly, one-fifteenth of the body weight. He then has 10 pounds of blood, which translated into cubic centimeters is approximately 5000 cc. Let us suppose that his hemoglobin percentage is 50. Suppose we transfuse him with 1000 cc (2 pounds) of blood containing 100 per cent of hemoglobin. Let us average the percentage the way a chemist does in making up solutions

$$\begin{array}{r}
 5000 \text{ cc at } 50 = 250,000 \\
 1000 \text{ cc at } 100 = 100,000 \\
 \hline
 6000 \qquad \qquad \qquad 350,000 \\
 350,000 \\
 \hline
 6000 = 58, \text{ the percentage of hemoglobin in}
 \end{array}$$

the patient's blood after the transfusion

The result perhaps is rather surprising. One would think that the transfusion of what seems like so large an amount of blood would give a much larger immediate rise in the hemoglobin than 8 per cent, but experience has borne out that calculation. As a matter of fact, most patients who have not arterial disease and whose hearts are not damaged can stand more than the 500 to 1000 usually given. Worm-Müller showed in 1875 that healthy dogs can actually stand a transfusion into them of as much as 80 per cent of their own blood volume (calculated at 14 per cent of the body weight). Crile's experiments also bear this out.

There is one additional and favorable point to mention in regard to the rise in hemoglobin percentage, namely that in practically all cases a subsequent rise in hemoglobin quite independent of new blood formation occurs within a period of one to three days after transfusion. This is supposed to be due to some process of concentration by elimination of excess plasma. It begins at once according to the observations of Botazzi

and Japelli in 1907, and was actually observed as long ago as 1875 by Lesser

One may see in the literature a good many warnings about acute dilatation of the heart from too large or too rapid transfusion. This danger undoubtedly exists, although the possibility of such an accident occurring is actually not very great. Dr. Unger's warning, that one should stop transfusing if the patient begins to cough (unless, of course, he has been suffering with a cough before the transfusion), is valuable and should be heeded. Furthermore, on general principles, in all transfusions the first 100 to 200 c c should be allowed to run in very slowly. In the case already cited, for example, in which there was a misunderstanding and a hemolytic donor was used, this precaution probably saved the patient's life, as the first symptoms of discomfort on the part of the patient were heeded and the transfusion was promptly stopped. In all transfusions, of course, the patient's appearance, general condition, and sensations should be watched closely, and anything untoward should be the signal to stop.

A point that the practitioner usually leaves to the specialist is the decision as to the method of transfusion to be employed. Of the numerous methods which have been introduced, two have withstood the test of time and large experience, these are (1) the syringe method, either in its original form as reintroduced by the late Edward Lindeman or in one of its modifications, such as the Unger apparatus, and (2) the sodium citrate method. Each method has its advantages, and those who do many transfusions should be prepared to use either method in suitable cases, but in the great majority of average cases the sodium citrate method is the method of choice because of its extreme simplicity and ease of performance. In fact, it is so easy to do a sodium citrate transfusion that every practitioner should at some time in his training learn how. Any one who is capable of giving an intravenous infusion is capable of learning, with very little trouble, how to do a citrate transfusion. Undoubtedly many lives would be saved and many sick persons benefited if doctors were to realize this.

The one undoubted disadvantage of the citrate method is that the chills which may occur after it are usually more severe and more likely to occur in a given instance than after a well-performed syringe transfusion. However, as these chills occur in only about 20 per cent of all cases and are usually harmless, this factor need seldom deter one. Nevertheless in extremely desperate cases of patients in a greatly weakened condition the danger of death from exhaustion in a severe chill has to be considered and may constitute an indication for the use of the syringe rather than the citrate method. The outstanding advantage of the syringe methods at present is the relative freedom from chills after transfusion. The disadvantage is that the syringe methods all require much apparatus, very expert operators, and a thoroughly organized team of assistants.

A question often asked is whether any special preparation of donor or patient is needed for transfusion.

For the donor, nothing is needed. He should not be allowed however to nerve himself up by the use of alcohol, as he is sometimes tempted to do. For the patient, usually there is no special preparation. The twelve hours' fast of donor and patient, by which it was hoped at one time one could avoid chills, has not in practice proved to have sufficient effect. In some chronic anemias, particularly those where there is hydremia or heart weakness, and in patients who have high blood-pressure, the so-called "drying-out" treatment, suggested by Dr Libman, is advisable in order to reduce the blood volume somewhat before new blood is introduced. It consists of keeping the patient on the Karrel diet (900 c c of milk with no other fluids whatever) for twenty-four or forty-eight hours and, if his condition permits it giving him a saline cathartic.

Finally, the question is always asked "Will the patient require any special after-care?"

Some competent person, nurse or physician, must always remain with him for an hour after transfusion in case he should have a chill and the ordinary stimulants and hot-water bags used for chills should be at hand.

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THE HEART IN THE TUBERCULOUS

The Size of the Heart in Phthisis, Functional Cardiovascular Disorders, Thyrogenic Cardiovascular Disorders; Displacement of the Heart; Valvular Heart Disease, Congenital Heart Disease, Myocarditis; the Right Ventricle, Pericarditis, Illustrative Cases of All These Groups

THE study of the heart in the tuberculous offers so many different phases that in a short presentation such as this one only a few of the important points can be emphasized. Tuberculous patients frequently complain of symptoms which they refer to the heart. The physician for his part, usually has very hazy notions as to the cause of these symptoms, and explains them by the use of conventional phrases which are rarely expressions of clear ideas of the underlying pathologic anatomy and physiology.

THE SIZE OF THE HEART IN PHTHISIS

Before we proceed with the discussion of the disorders of the heart that may become manifest in the tuberculous it will be well to consider whether any particular type of heart predisposes to tuberculosis, or is found with exaggerated frequency among tuberculous subjects. This problem alone has been the cause of many discussions and researches the results of which, however may be briefly summarized.

Lacnec in 1819 was one of the first to note the frequency with which a small heart was found on autopsy in tuberculous individuals. Louis Potain, Stokes, Rokutansky and Benecke are among the prominent physicians of the 19th century who con-

firmed this finding. However, in the interpretation of its significance there has been a great conflict of opinion. Some, such as Rokitsky and Benecke, believed that a small heart and small arteries were associated with the tuberculous habitus, that they comprised a primary constitutional anomaly which caused a predisposition to tuberculosis. Others, again, claimed that the heart was small because it shared in the atrophy of the skeletal musculature which is so universal in all victims of phthisis. More recent investigations carried out with greater precision have thrown more light on the subject. The chief criticism that may be leveled at the dicta of these earlier investigators is that they studied the hearts of patients who had died from the disease, and assumed that at the beginning of the illness the heart was just as it appeared at autopsy.

Orthodiagraphic studies of the heart of patients with early tuberculosis reveals many whose size is normal, although some, it is true, are small. Hirsch, whose determinations of heart size are very accurate, found that the small heart in patients with advanced tuberculosis was not constitutional, but ran parallel to the emaciation of the body musculature. Norris,¹ out of 1269 autopsies on tuberculous subjects in which the heart was weighed, found 707 hearts normal in size, and only 184 underweight. Where, then, is the truth amid all of these conflicting reports and opinions? Just as we have gradually learned that there is no such thing as a recognizable tuberculous habitus that predisposes to tuberculosis, but that this same habitus is found among many non-tuberculars who fall under the general description of asthenic individuals, we must learn that heart size and shape does not predispose to tuberculosis, and that the same small heart which has been thought characteristic of tuberculosis occurs as well in non-tuberculars. Some tuberculous patients, especially those with narrow chests, have a small heart at the onset of the disease, but there is no proof that this has predisposed to the disease. Patients who die of phthisis often have a heart which has become small from wasting. It is important to grasp these fundamental facts, for they will enable us to understand that some cardiovascular symptoms of

tuberculosis are not peculiar to this disease, but are common to all individuals who are endowed at birth with similar hearts

FUNCTIONAL CARDIOVASCULAR DISORDERS

Palpitation, precordial pain, and dyspnea on exertion are probably the most frequent complaints referable to the heart to which tuberculosis patients are subject. These may be due to a number of different causes. A few cases will be presented to illustrate these different groups

M P Female Age twenty-three

Family History—No tuberculosis or cardiovascular disease. Patient's mother has always been rather frail and nervous. She worries much, and in times of stress and excitement "goes to pieces."

Past History—No acute illness except for the common diseases of childhood. Patient has always been a high-strung, active girl. One month ago she began complaining of sudden attacks of vertigo and palpitation, which at times were followed by fainting. These came on when she had been on her feet a long while. With this there was increased nervousness and frequent palpitation. Gastro-intestinal symptoms of epigastric oppression, pain, and occasional vomiting also became manifest.

Physical Examination—The patient is a tall, narrow-chested individual of typical asthenic build. The heart presents no abnormalities to physical or x-ray examination. The pulse is of good quality, its rate 100. Blood-pressure 110/75. There is a moderate visceroptosis. The hands are rather cold and moist and slightly cyanotic. The lungs show bronchovesicular breathing, dullness, and moist râles at the left apex. Sputum contains tubercle bacilli.

Such a clinical picture is seen not infrequently early in a case of tuberculosis, and some or all of these symptoms are often observed during the later course of the disease. These vasomotor, dyspeptic and asthenic symptoms, to which for convenience I shall refer as neurasthenic, are not peculiar to tuberculosis. It is a well-established fact that they are often signs of constitutional nervous instability, which is not infrequently an

hereditary trait. Several authors have emphasized that neurasthenic symptoms in tuberculosis are particularly evident in patients with such a constitutional nervous predisposition. Jessen² says that lability of temperament and similar symptoms in tuberculosis are more pronounced in individuals with a poorly organized psychic nature, and that the neuroses in tuberculosis are due to the action of the toxin on a congenitally weak nervous system. The best paper that deals with this subject is by Muralt.³ He considers all of the vasomotor and dyspeptic phenomena that one encounters in the tuberculous, as well as the fatiguability and lack of will power, and finds that a constitutional nervous predisposition is very important in the development of all of these symptoms. He further states that phthisis may activate a latent neurasthenic tendency. In the discussion of this paper Dubois,⁴ too, emphasizes the importance of a constitutional neurasthenia underlying the nervous symptoms manifested by tuberculous patients.

The resemblance between these patients and those with the syndrome known as neurocirculatory asthenia is very apparent.⁵ The symptoms and physical signs are the same in both groups. In both diseases we are able to classify our patients into those with constitutional nervous instability, and those in whom the symptoms have followed an infection. In the constitutional group of neurocirculatory asthenia an infection always serves to aggravate the symptoms, and not infrequently latent symptoms are first brought to light after an acute febrile attack, such as pneumonia. Chronic infections may act in the same way. A careful history of phthisical subjects will reveal in some of them mild nervous, vasomotor, and gastro-intestinal symptoms, antedating by many years the tuberculosis. In other cases these symptoms make their very first appearance with the disease. Is it not probable, then, that those cases of tuberculosis which are ushered in with such striking cardiovascular symptoms really belong to the neurocirculatory asthenia group, and that in them the tuberculosis acts as the acute infection, bringing to light latent symptoms? It is striking, too, that the so-called tuberculous habitus is encountered frequently

among patients with neurocirculatory asthenia. Those cases with a negative history, in whom the symptoms develop during the course of the disease, are comparable to the second type of neurocirculatory asthenia. Functional gastro-intestinal disorders act in the same way as the cardiovascular ones. This is true both of cases of neurocirculatory asthenia and of tuberculosis.

The patient whose history has just been presented had a latent constitutional nervous and vasomotor instability, which was activated by the development of the tuberculous infection. She would have presented the same cardiovascular symptoms after an attack of influenza or pneumonia.

THYROGENIC CARDIOVASCULAR DISORDERS

Another group of tuberculous patients presenting a rather similar cardiovascular symptomatology are those who exhibit, in addition to their pulmonary infection, symptoms, more or less marked, of Graves' disease. The frequent association of these two disorders, particularly in women, has often been remarked. The prominent symptoms are enlargement of the thyroid, exophthalmos with associated eye signs, tachycardia, vasomotor instability, palpitation, nervousness, and tremor. Most authors believe that the occurrence of these symptoms is of good prognostic import as far as the progress of the tuberculous lesion is concerned. The following case illustrates the type under discussion.

B K No 2003 Female Age twenty-two

Family History — Unimportant

Past History — Negative, except for pertussis in childhood. Menses normal.

Present Illness — Began six months ago with a dry hacking cough day and night. After a few weeks fever was observed, the patient became weaker, breathless occasionally, and at times complained of palpitation. All of these symptoms have continued.

Physical Examination — The patient is a fairly well-nourished girl. The eyes are prominent and a Von Graefe sign is present.

There is a moderate general thyroid enlargement. The lungs show dulness and bronchial breathing over the right upper lobe, and flatness and intense bronchial breathing at the right base, with very few râles. Left lung normal. Aspiration of the right chest revealed no fluid. Heart appears small on physical examination. Pulse of good quality, rate 120 to 140. Blood-pressure 125/70. Slight tremor of hands. There is slight acrocyanosis. The temperature on admission ranged about 101° F. In two months it became normal, but the rapid pulse-rate persisted.

x-Ray shows advanced infiltration throughout the entire right lung field, with multiple small cavities at the apex. Left lung clear, heart abnormally small.

Electrocardiogram shows left ventricular predominance. Urine normal except for a faint trace of albumin. Sputum shows tubercle bacilli.

It seems probable that in this patient the cardiovascular symptoms were due to the hyperactivity of the thyroid gland. By no means all of this class of patients present so clear-cut a symptom-complex. In many it is difficult to classify the symptoms, and to know whether or not to relate them to a disorder of the thyroid gland. Many of the patients with symptoms of hyperthyroidism show no evidence of left ventricular predominance electrocardiographically. The epinephrin test is of no value in the study of these cases, for it may be positive when there is no evidence of thyroid disease.

DISPLACEMENT OF THE HEART

In patients with advanced tuberculosis cardiac displacement is one of the most frequent causes of palpitation, dyspnea, and precordial pain. Over 75 per cent of far-advanced, and 40 per cent of moderately advanced cases show displacement of the heart. When there is much destruction of pulmonary tissue, with cavitation and shrinkage of the lung, the heart is pulled to the side of the most extensive lesion.⁶ This is brought about by pleuropericardial adhesions. Displacement to the left is more frequent, but right-sided dislocation occurs as well.

The phenomenon appears most commonly in chronic fibroid phthisis. At times the displacement is prevented by adhesions on the opposite side. All degrees of dislocation may occur. There may be a complete dextrocardia or again the left border of the heart may be found in the axilla. This is not sufficiently emphasized in the text-books. Not infrequently because the physician finds the left cardiac border beyond the midclavicular line, and the heart thrust apparently exaggerated because of the retraction of the covering lung tissue cardiac hypertrophy is diagnosed. The following case is illustrative.

M. H. No. 39143. Female. Age twenty-one.

Family history and past history are unimportant.

Present Illness—Began four years ago with anorexia and loss of strength, afternoon flushes, and headaches. There were frequent sweats noticed particularly on awakening in the morning. Soon a cough developed which at first was dry and hacking, and associated with pains in the chest and later became productive. For two years the patient stayed in the country and slowly improved. She then went to Denver, where she stayed thirteen months. She was febrile while there. Tuberculin injections were given for two months during which time she lost 20 pounds in weight. On admission to the Montefiore Hospital four years after the onset of her illness she was complaining of cough and expectoration, night-sweats, weakness, and loss in weight. In addition for the last six months or so there had been increasing dyspnea on exertion, frequent palpitation and pains in the left chest over the precordial area.

Physical Examination—The patient is a young girl, fairly well nourished with marked retraction of the left supra- and infraclavicular fossæ.

Lungs There is infiltration of the whole left lung with a large cavity in the upper lobe. The left dome of the diaphragm descends very little on inspiration. There is infiltration of the right upper lobe.

Heart There is an exaggerated cardiac impulse over the fourth and fifth inter-spaces extending a little beyond the midclavicular line. The impulse is not very forcible. The left

border is about $1\frac{1}{2}$ cm to the left of the midclavicular line in the fifth interspace. The right border is at the midsternal line. Sounds normal, no murmurs.

Pulse Small, regular, rate 96

Blood-pressure 108/68

Temperature Diurnal variations from 100° to 101° F

Respirations 24 to 28



Fig 162—Displacement of the heart to the left in advanced pulmonary tuberculosis

Sputum shows tubercle bacilli

Urine normal

The x-ray plate (Fig 162) shows the cardiac displacement, as well as the pleuropericardial adhesions very clearly. It is in such a case that one must beware of being misled by the symptoms referable to the heart, and by the abnormal cardiac impulse, in diagnosing an organic cardiac lesion.

VALVULAR HEART DISEASE

Rokitansky in 1846 first established the dictum that disease of the valves of the left side of the heart and pulmonary tuberculosis were antagonistic, and rarely occurred simultaneously. Ever since there has been much study and discussion to prove or disprove this statement. In studying the immense literature which has grown up on this subject there are several criteria which we must be careful to apply. Most of the reports are based on autopsy studies. Cases presenting only small healed tuberculous lesions should be ruled out, for such a finding is almost universal among adults, and has no bearing on the problem of the frequency of association of valvular heart disease and active tuberculosis. Only frank valvular lesions should be included, and not every case with slight roughening of the valves termed "valvular heart disease." It is because of the fact that many authors have not considered these points in studying their material that the reports are so at variance with one another. However, a sufficient number of accurate studies remain.

Sauer,⁷ in a series of 304 autopsies on patients with mitral disease and chronic passive congestion of the lungs, found $3\frac{1}{2}$ per cent with active tuberculosis. In his general series of autopsies tuberculosis was the cause of death in 15 per cent. This study is but one of many which I quote to show that tuberculosis and valvular disease may occur together, but that their association is rather infrequent. Sauer further concludes from his study that, among all the valvular lesions, mitral stenosis is most infrequently associated with tuberculosis. He believes that a mitral insufficiency which is accompanied by a brown induration of the lung, gives a certain immunity to tuberculosis. The advance of an existent tuberculosis is not, however, modified by the presence of a heart lesion, but the lung disease exerts an unfavorable influence on the reserve power of the heart. Fossier⁸ expresses similar views. Brown⁹ emphasizes the fact that the valvular disease is usually the primary condition. He has never seen it develop in the course of a tuberculosis. A true tuberculous endocarditis is so rare

that it need not be considered. It can only exceptionally be diagnosed during life.

My own experience on the Tuberculosis Service of the Montefiore Hospital confirms these observations. The association of tuberculosis and valvular disease is infrequent, but does occur. One must, however, beware of interpreting every murmur as a sign of valvular disease. Functional murmurs both at the apex and base are of frequent occurrence, and when they are associated with cardiac displacement may be deceptive. Definite cardiac hypertrophy or the history of an acute rheumatic infection are usually prerequisites to the diagnosis of a valvular lesion. Accentuation of the pulmonic second sound is rarely of value in differential diagnosis. Consolidation or retraction of the lung in the second left interspace is very common in tuberculosis. Such a condition, of course, will cause apparent accentuation of the second pulmonic sound due to its more ready transmission to the chest wall.

In the presence of frank organic heart disease pulmonary tuberculosis should not be rashly diagnosed. Many a time a little dulness, associated with râles over an upper lobe, and a little fever give rise to the suspicion that tuberculosis accompanies the heart disease. Unless the lung signs are very definite and persistent, or tubercle bacilli are found in the sputum, the diagnosis of tuberculosis is unwarranted. Such signs usually clear up as the cardiac condition improves. In such cases x-ray plates too may be deceptive. The diffuse mottling of the lungs due to the congestion is frequently mistaken for tuberculous infiltration. An aneurysm compressing a bronchus may cause extensive lung signs, which are often incorrectly interpreted. Finally, it is well to remember that hemoptyses occur in pure cases of mitral stenosis, and in such cases are no indication of an accompanying tuberculous infection.

In summary we may say that, although heart disease and pulmonary tuberculosis do at times occur together, we must always make such a diagnosis with hesitancy, and only after we have proved it beyond cavil.

The following case shows how difficult this is at times

B H No 40 830 Female Age fifty-three

Past History—Pneumonia at fifteen years No rheumatic fever, chorea, or tonsillitis

Present Illness—Cough for several years One year ago nosebleeds began, which occurred every few weeks, and were brought on by hard work or excitement One year ago the cough became worse and she was told that she had tubercu-



Fig 163—Hypertension, cardiac hypertrophy, auricular fibrillation, and pulmonary tuberculosis This picture has been printed reversed The heart should be pointing to the left

losis Of late she has complained of night-sweats and weakness One month ago her feet became swollen and dyspnea became marked

Physical Examination—The patient is a well-nourished woman, slightly cyanotic, with dyspnea and some orthopnea

Lungs Dulness and many moist rales at both bases posteriorly below the scapular angle In the right supraspinous fossa

there is dulness, marked bronchovesicular breathing, with moist râles on inspiration

Heart Left border 12 cm to left of midsternal line, in fifth space Right border 4 cm to right of midsternal line First sound good Aortic second sound accentuated There is a systolic murmur at the apex Action absolutely irregular, rate 120

Pulse Absolutely irregular in force and rhythm Rate 100

Blood-pressure Most beats are heard at the level of 190 mm of mercury

Abdomen Fat and pendulous Liver felt 6 cm below costal margin

Extremities Moderate edema of legs below the knees

Urine At times shows trace of albumin and a few casts

Temperature normal

x-Ray See Fig 163

In this case the cardiac symptomatology was so definite that it appeared probable that all of the physical signs could be explained on this basis However, sputum examinations repeatedly revealed the presence of tubercle bacilli Without this positive finding the diagnosis of tuberculosis would have been unwarranted The case is interesting from another point of view The cardiac condition was apparently secondary to a hypertension, and hypertension is rare in tuberculosis

CONGENITAL HEART DISEASE

The relationship between phthisis and some congenital heart lesions is of interest Lebert¹⁰ in 1867 first called attention to the relative frequency with which congenital pulmonic stenosis is followed by pulmonary tuberculosis In fact, most children with this heart lesion who survive their tenth year die of tuberculosis The manner in which stenosis of the pulmonary orifice predisposes to tuberculosis is a matter for speculation The following is such a case

S L No 1735 Female Age fifteen

Family History—Negative for tuberculosis and heart disease

Past History—Scarlet fever at seven years of age Patient was in bed for six weeks at this time and her cardiac condition was then first noted Cyanosis and clubbed fingers as long as she can remember She has always been short of breath on exertion No edema In cold weather her lips would get very blue

Present Illness—Fourteen months before admission to the hospital she coughed up 3 cups of blood This was followed by



Fig 164—Congenital pulmonic stenosis and pulmonary tuberculosis This picture has been printed reversed, what is right should be left, and vice versa

cough, fever and night-sweats, and blood-streaked sputum These symptoms have persisted off and on ever since

Physical Examination—The patient is poorly developed for her age, and weighs 70 pounds There is marked cyanosis The fingers show very much clubbing

Lungs Infiltration of the right upper lobe with dulness at the left apex

Heart Markedly enlarged to the right and left There is a long, rough systolic murmur heard loudest at the pulmonic area and transmitted over most of the chest

Pulse Small, rate 110 to 120

Blood-pressure 100/60

Sputum Tubercle bacilli present

x-Ray See Fig 164

This patient became progressively worse after her admission to the hospital and died from an influenzal bronchopneumonia

MYOCARDITIS

Myocarditis is often diagnosed in phthisical patients, but it is rarely found on autopsy Physicians have acquired the habit of explaining all kinds of symptoms on the basis of a myocarditis Many of these symptoms are very common in tuberculous patients and so the clinical diagnosis of myocarditis is often made It is important to know that precordial pain, dyspnea, rapid heart action, a small pulse, low blood-pressure, and faint heart sounds do not necessarily give any indication of myocardial disease Many of these symptoms, it will be recalled, occur in the functional disorders of the heart, which were discussed above The diagnosis of myocarditis is justifiable only when there is a history of an acute infection followed by cardiac disturbance, or when cardiac hypertrophy, a significant irregularity, or myocardial insufficiency give definite indication of disease of the heart muscle

The rapid pulse of patients with tuberculosis has given rise to much speculation and discussion Tachycardia is one of the classical symptoms of phthisis, and may appear at a very early stage of the disease To a certain extent it parallels the severity of the infection, but many inactive cases may still show a persistently rapid pulse Another characteristic sign is the marked lability of the pulse The rapid, labile pulse of tuberculosis may at times be explained on the basis of some of the types of cardiac affection noted above Chief among these are the neurocirculatory asthenic type, the hyperthyroid type cases, and those with cardiac dislocation Some authors have en-

deavored to attribute the tachycardia to involvement of the vagus or the sympathetic by tuberculous glands in the mediastinum. Others have laid the blame on the toxemia of the disease. While a rapid pulse in tuberculosis is not always of bad import, a slow one is a good prognostic sign.

The same general point of view is applicable to the blood-pressure. A low blood-pressure is very constant in the tuberculous and does not necessarily presage a poor prognosis. Many asthenic individuals who have no lung disease have a persistently low blood-pressure. On the other hand a normal or a high arterial tension usually indicates a mild or inactive tuberculosis.

THE RIGHT VENTRICLE

It has been generally assumed that in chronic phthisis there is frequently found a dilatation or a hypertrophy of the right ventricle. This is explained usually by the assumption that with extensive pulmonary disease there is a partial obliteration and obstruction of the pulmonary stream bed, which exacts an increased amount of work from the right ventricle to maintain the circulation. This mechanism would be analogous to the left ventricular hypertrophy that accompanies arterial hypertension. On analysis the evidence for this belief is found to be conflicting and for the most part inadequate. Lichthem¹¹ showed that obliteration of the pulmonic stream bed leads to dilatation and hypertrophy of the right ventricle only when three-quarters of the stream bed is shut off. So one would expect to find enlargement of the right chamber of the heart only with extensive lung disease. Careful postmortem studies confirm this opinion. Both Hirsch¹² and Wideroe¹³ found right ventricular hypertrophy in about 35 per cent of patients who had died from pulmonary tuberculosis. The degree of hypertrophy paralleled the extent of the pleural adhesions and fibrosis of the lung.

In view of these findings reported in the literature, and of theoretic consideration which suggested that there was some physiologic basis for the changes that had been described, Dr. Hubert Mann and I made an electrocardiographic study of a

series of tuberculous patients, in the hope that by this means we might be able to determine whether or not there was a predominance of one of the chambers of the heart¹⁴ At the same time the case was studied in order to correlate the electrocardiographic with the clinical findings The results may be briefly summarized

An electrocardiographic study of 97 patients with pulmonary tuberculosis revealed 29 per cent with right ventricular predominance, 30 per cent with left ventricular predominance, and 41 per cent with predominance of neither chamber Right ventricular predominance is not always associated with any particular type of tuberculosis It is found more commonly in young than in old patients, and twice as frequently in men as in women Left ventricular predominance is not always associated with any particular type of tuberculosis It is found more commonly in older patients, and is twice as frequent in women as in men Left ventricular predominance occurs more frequently with the increasing age of the patient In contrast to the autopsy findings reported in the literature, right ventricular predominance is not found more frequently in association with fibroid phthisis, or with pleural adhesions, than with other types of pulmonary tuberculosis

These results make it apparent that the electrocardiograph at present is of little clinical value in the study of the heart of tuberculous patients Further studies should, however, be made to explain the discrepancies noted above

PERICARDITIS

It is well to recall that tuberculous pericarditis is a rather frequent complication of phthisis Norris¹ found it in 4.4 per cent of a series of 1780 autopsies on tuberculous subjects Very often there are no symptoms that suggest involvement of the pericardium, and it is only by bearing constantly in mind the possibility of this complication that we may succeed in diagnosing it during the life of the patient

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THE GENERAL MANAGEMENT OF FUNCTIONAL DIGESTIVE DISORDERS

Definition and Incidence of Functional Digestive Disorders, Attitude of the Physician to the Patient, Putting the Patient's Mind at Rest, the Value of Rest and Routine, Dietary Indiscretions, Food Restrictions; the Manner of Eating, Tachyphagia, its Treatment, Drug Therapy, Neurosis in Asthenics, its Management; Surgery in Neurosis and Asthenia, Illustrative Cases

FUNCTIONAL disorders of the digestive tract may be defined as disturbances of the nerve control of digestion—whether sensory, motor, or secretory in nature—arising independently of gross lesions of the organs involved in the process. The chief interest in this subject ordinarily centers, quite properly perhaps, about the question of differential diagnosis from the organic lesions which these disorders so closely resemble. Once organic disease is ruled out, however, the neurosis is by no means invariably relieved forthwith. Sometimes a cure, even under the best of care, is unfortunately unattainable, but only too often the patient makes no progress, either because of lack of knowledge or of interest on the part of his doctor, or because he is treated in what might be called a spirit of piqued reprisal as though, having originated his disorder within himself, he ought to proceed to repair it unaided.

And yet there are good reasons why such patients should always receive serious attention. Indeed, by their very numbers they compel consideration. The overfed, the hungry, the

overworked, the idle, the genius, the drudge—all help to make up the many-sided picture of functional digestive breakdown. Wherever there is anxiety, or worry, or remorse, or care, or indeed, any mental anguish, there, among the first of physical failings, is nervous indigestion. In our war-time army, at least one-third of the men hospitalized for digestive complaints suffered from neurosis, while among the civilian population one is always being impressed by the great numbers of functional cases seen not only in the dispensaries and private practice, in hospital wards and sanatoria, but unrecognized and uncounted, in the crippled and unhappy pursuit of their daily occupations.

To one familiar with these facts it should be self-evident that a fundamental principle in dealing with functional disorders is to treat the patient behind the disease. Whereas, in an organic condition, we focus directly on the organ or lesion in question, in the neuroses, we reverse the binocular, so to speak, add distance to the perspective, and include the whole patient, his mental as well as his physical background, and as much of his environment as is possible. Obviously it would be futile to attempt to discuss in detail all the possible methods whereby such a plan could be put into practice. Rather is it my purpose to bring out certain general principles underlying the successful management of these neuroses. Let us begin, then, by considering the attitude of the physician to the patient.

Neurotics as a class are sensitive and emotional, and their first impression of the doctor often decides his usefulness to them. Conversely, the management of the patient really begins with his examination, and it is therefore doubly important that the proper note be struck on this occasion. Obviously, the examination must be thorough, otherwise the diagnosis of functional disorder would be untenable. Moreover, it should be comprehensive enough to include any possible defects whose correction would serve to improve not only the physical but the psychic well-being of the patient. If, in addition to its completeness, the examination is sympathetic and reassuring in manner, the seeds are sown for that welcome feeling of confidence and faith which spells, more than anything else, success.

in treatment. Once gained, this relationship must be assiduously cultivated by the physician on every occasion. In no other kind of work does and should he so literally minister to his patient, in mind as well as in body.

Just as, in organic conditions, we try to spare a diseased part or organ by rest of its function, so it is essential, in treating neurosis, to put the patient's mind at rest. In the ordinary simple case this is well accomplished by giving the patient a proper insight into his condition. To tell a neurotic individual that there is nothing the matter with him does not always work. For one thing, it is not true, besides, it is not satisfying. On the other hand, peace of mind through insight doeth good like a medicine. Many a patient (to say nothing of medical students) has been started on the mend by being told that he has nervous indigestion instead of ulcer of the stomach, and even an unintelligent person can understand and appreciate the difference between trouble due to a broken-down machine (organic disease) and trouble due to a crazy driver (functional disorder).

In the more complicated cases, where the neurosis is due to some cause beyond the power of the physician to control—such as worry over family or money matters—the utility of this procedure may seem more limited. And yet even here it is not without value. Where the relation between cause and effect is not clear to the patient, the result of this knowledge may be sufficient to produce a “psychoanalytic cure” in the manner already described. If, however, the patient has diagnosed his case beforehand, the authoritative confirmation of his views will reassure him, will strengthen his morale. In short, will put him in far better shape to take advantage of whatever other measures—such as sedatives—the physician may employ to help break the vicious circle.

So much for the purely psychic element in our problem. Where the neurosis is brought about by sheer mental or physical overexertion, rest can best be secured by retirement from the harmful occupation, with, when possible, a change of scene and activity. In the milder cases satisfactory results may be

obtained by relaxation after meals, by plenty of sleep (especially in the asthenics), and by simple and regular feeding. In the severer cases, where persistent pain is complained of, nothing short of bed rest may suffice. This, with complete isolation, forced milk feeding, and special re-educative measures, is the method so successfully employed by Weir Mitchell and some of the French neurologists. In this, as indeed in any set method of treatment, the value of routine cannot be overestimated. The classic neurotic is notoriously unstable, and it is by the practice of consistent hygienic habits that the value of order, poise, and moderation in the conservation of health can most effectively be inculcated.

Dietary indiscretions constitute an important factor in the production of digestive neurosis. Perhaps the majority of people, healthy as well as dyspeptic, have learned to avoid foods known to be difficult of digestion, such as sour and spicy things, fats, sweets, and the tougher meats and vegetables. Yet there are some who, despite the onset of symptoms, seem never to have acquired this knowledge. Thus, I have before me the record of a woman whose daily bill of fare consisted of coffee and cake at 11 o'clock, oysters at 2, candy at 3, ice-cream at 4, and coffee and French pastry at 6. Another lady once told me that as a girl she took every day at luncheon 1 cupful of vinegar, and that she continued this practice for almost two years before it was interrupted.

In contrast to the above, however, it is by no means uncommon to find that the neurotic dyspeptic has eliminated one article after another from his diet not because he has found them to disagree, but from some totally extraneous reason. This psychic phagophobia can generally be traced to some popular science article, or fad, or neighborhood gossip, or to the ubiquitous advertisement. So impressed are these people with the necessity of self-mortification through dietary restriction that the recommendation of a liberal, well-balanced fare is often met with surprise if not with anxious opposition. Such patients should naturally be vigorously taken in hand and be made to retrace their course until they can once more eat with relish.

and impunity every thing that they could handle before the onset of symptoms

Incidentally, it may be remarked that the manner of preparing the food should also be given some attention, more perhaps than it is ordinarily accorded. Obviously, the best of food can be spoiled by poor cooking. Perhaps the chief sufferers from this cause are those who are forced from reasons of economy or other necessity to "eat out" in the poorer restaurants or "on the road" while traveling for business.

Far more important, however, than the kind of food or its preparation, is the manner in which it is eaten. The plan of eating three meals a day, with breakfast, say, at 8, lunch or dinner at 1, and dinner or supper at 7 has the advantage of allowing a sufficient time to elapse between meals for a reasonable amount of digestion to take place in the intervals. As a matter of fact, the stomach is seldom empty except before breakfast but experience shows that the normal individual is quite able to take care of his food on this basis. With meals taken on time, the digestive tract is aided in carrying on its functions by the factor of routine or habit, as already suggested. Hunger, appetite, satiety, food intake, and waste output recur in their normal regular rotation. So closely linked are the digestive processes that but a single break in the chain may suffice to upset the usual sequence, and this likelihood increases to certainty in the case of the hypersensitive patient.

Other factors than promptness at meals are desirable for the maintenance of good digestion. Every one knows how food eaten under disturbing or depressing conditions lies heavy on the stomach. Similarly, a preoccupied state, such as that of the business man at lunch time, hardly serves as an aid to digestion. To be sure, the eating of food is in a sense a mechanical process based on habit, yet it is important that proper habits of eating be learned from the beginning—obviously a job for pediatricists and parents—that these habits be maintained through life and that bad habits be not developed. A certain amount of attention to the business in hand is essential, therefore, to proper eating, and this cannot obtain when the individual is preoccupied or

hurried Under such circumstances there arises only too often perhaps the worst and certainly the most intractable of bad eating habits—tachyphagia It was Napoleon's proud boast, I believe, that while other generals feasted for hours, he spent but a few minutes at his meals, and there can be no doubt that rapid eating is a fault, not of the sluggard and the unambitious, but of the quick, keen, and energetic in mind and body Since we Americans are quite likely to suffer from these faults as well as these virtues, it may be profitable to quote here the following suggestive description of a scene in a New York boarding house as given by Charles Dickens in his "Martin Chuzzlewit" (1843)

"It was a numerous company—eighteen or twenty, perhaps All the knives and forks were working away at a rate that was quite alarming, very few words were spoken, and everybody seemed to eat his utmost in self-defense, as if a famine were expected to set in before breakfast time to-morrow morning, and it had become high time to assert the first law of nature The poultry disappeared as rapidly as if every bird had had the use of his wings, and had flown in desperation down a human throat The oysters, stewed and pickled, leaped from their capacious reservoirs, and slid by scores into the mouths of the assembly The sharpest pickles vanished, whole cucumbers at once, like sugar-plums, and no man winked his eye Great heaps of indigestible matter melted as ice before the sun It was a solemn and an awful thing to see Dyspeptic individuals bolted their food in wedges, feeding, not themselves, but broods of nightmares, who were continually standing at livery within them Spare men, with lank and rigid cheeks, came out unsatisfied from the destruction of heavy dishes, and glared with watchful eyes upon the pastry What Mrs Pawkins felt each day at dinner-time is hidden from all human knowledge But she had one comfort It was very soon over "

Dicken's genial spirit must indeed have nodded approval when, some twenty years ago, an American layman, as vice-president of the Food Reform Society of England, called widespread attention to the possibility of improving men's eating habits Horace Fletcher's activities made an impression not

only on the public but in medical circles as well. As a result, various studies were undertaken with the purpose of showing objectively the dangers of tachyphagia. It was claimed, and in part proved, that this habit interfered with the proper subdivision and insalivation of the food, that it favored air swallowing globus and the development of esophageal spasms and diverticula, that it increased the work of the stomach, that it raised the body temperature and the blood-pressure, and that it interfered possibly, though very slightly, with the utilization of certain food-stuffs. The fact that many rapid eaters live comfortably for years shows that the dangers of this habit may indeed be overrated, yet it is equally true that when the rest of the digestive tract is called upon vicariously to undertake some of the work that should properly be done in the mouth, the chances of its breaking down are correspondingly augmented.

The successful treatment of tachyphagia is very often no easy matter. It demands not only patient and persistent attention to detail on the part of the physician but also the serious and willing co-operation of the patient. To begin with, it may be wise to insist on a minimum period of time for each meal, such as three-quarters of an hour for lunch and an hour for dinner. In order to avoid the secondary danger of over-eating, a definite amount of food should not be exceeded. A fortunate natural safeguard in this direction exists in the fact that those who have learned the art of careful chewing find themselves satisfied with less food than they did as rapid eaters. It is well to select those articles which require thorough mastication, such as the drier and more resistant food-stuffs, and the drinking of fluids, especially when used, as often, to wash down mouthfuls should be studiously avoided. In the more obstinate cases it may even prove necessary to provide an attendant to assist the execution of these orders by personal supervision.

A word as to drug therapy. Local treatment, such as with antacids and antispasmodics, is often beneficial and may indeed be necessary, just as one would use direct intragastric measures—lavage or aspiration—when these are indicated. It should not be forgotten, however, that local symptoms tend to dis-

appear as nervous stability is restored to the patient, and that this end can very well be accomplished (so far as medication is concerned) by the use of systemic sedatives, such as bromids, codain, and the somnifacients. Where general hygienic measures cannot well be carried out, as in dispensary practice, and in virtually all cases at the beginning of treatment, these drugs are, indeed, almost indispensable. On the other hand, the use of "tonics," such as strychnin, can hardly be recommended. Whipping a jaded horse is never good practice. It is much better to wait for the renewed strength and vigor that is bound to come from a refreshed and rested mind and body.

Neurosis in asthenics deserves more than casual consideration. By asthenics we mean those individuals who, owing to their congenitally weak body structure, are at a constant disadvantage in carrying on the affairs of life. Physically they are characterized by the so-called *habitus enteroptoticus*. The chest is long and narrow, the scapulæ are winged, the ribs flare down, the subcostal (epigastric) angle is acute, the xiphoid process is soft, thin, and receding, or quite impalpable, the tenth ribs are floating (Stiller's sign), the waist is narrow, the hips disproportionately wide. When standing, the whole body slouches, the shoulders are thrown forward, and the lower abdomen is prominent.

Corresponding to this external body form the viscera assume characteristic shapes and positions. The heart is of the median or drop type, the stomach and colon are long and reach low into the pelvis, the kidneys and liver, and not infrequently the spleen, are ptosed and palpable. There is diminished intra-abdominal pressure and a wide-spread atony of the hollow viscera. Prominent among the many subjective symptoms is a sense of weight or dragging in the stomach, and of pain in the back, whereas the general sluggishness of visceral function is well illustrated by the almost universal "chronic" constipation.

Such individuals feel always weak and tired, and they fatigue still more on the slightest exertion. If questioned especially as to their sleep requirements, it will be found that they need nine, ten, or more hours of repose nightly, instead of

the generally accepted eight-hour average for "normal" people. When as often happens, they are mentally active and ambitious they feel their physical incapacity as a particularly bitter affliction. In short, though not sick enough to give up entirely, they are not well enough to "carry on" as they would wish, and being often misjudged and "misunderstood," they are very likely to become increasingly wretched and despondent.

Once the essential nature of this disability is grasped, the principles governing its treatment become obvious. Radical reconstruction would suggest itself as the ideal procedure, and indeed something can be done in the way of changing the shape of the body. Special developmental exercises have been shown to be of value in widening the capacity of the lower thorax, a rugged outdoor life with complete freedom from care may accomplish the same purpose. But these are methods that are available to but few, and the results are distant. What the average asthenic wants is immediate relief from special symptoms. Besides, only too often he must keep on working. In such cases, then, it is best to accept the disability as a fact, certainly for the time being. An immediate estimate should be made of the patient's reserve and he should be ordered to keep his activities well within his limits. Especial attention should be given to the question of sleep, as already suggested, and, in fact, as much rest as possible should be taken in the recumbent posture, inasmuch as ptosis and its symptoms tend to disappear when the patient is reclining. Wherever possible, complete bed rest for at least two weeks should initiate the treatment, and with this should be combined forced feeding as will be described later.

The next therapeutic effort should be directed toward overcoming the ptosis and the intra-abdominal laxness. It is now generally admitted that this cannot be done satisfactorily by surgery, it having been found that most of the uplifted organs returned sooner or later to their original low standing. What is necessary is a more fundamental therapy aimed at correcting the underlying physical failings. This end can be accomplished from the exterior by means of devices tending to compress the lower abdomen back against the spine in such a manner as to

close off the pelvis from the abdomen proper and force the abdominal viscera back up where they belong. Such devices fall into three groups: adhesive strapping, abdominal binders, abdominal corsets. They should all be applied with the patient reclining. In deciding which particular type of support to employ in a given case the following points may be considered. For temporary purposes, or as a therapeutic test, adhesive straps are satisfactory. They require some skill in application, however, are not acceptable to patients with delicate skins, and necessitate complete renewal every ten days or two weeks. Nowadays good binders and corsets are readily available. They should always be fitted to the individual patient. Abdominal binders have the advantage of being light in weight and relatively inexpensive, but they will slip up when the patient moves about unless prevented by proper adjustments. Perineal straps or thongs are objectionable. The best models (such as the "Storm" or "Richardson") have flaps coming down on the thighs in front and connecting with an adjustable strap encircling each limb at the crotch. Corsets (such as the "Barnum-Van Orden" or "Roso") can be made to combine considerable style with excellent support and comfort.

It need hardly be pointed out that all the above measures are, in a sense, makeshifts. True, a binder or corset can be worn for years in absolute comfort, but so long as the fundamental atony remains uncorrected the original symptoms will return just as soon as the external support is withdrawn. It is here that the general reconstructive measures already mentioned can be brought into action, here also, another and perhaps more rapidly effective, and certainly more generally available, factor can be introduced in the treatment. It is well known that fat is accumulated not only externally but internally as well, and it is easy to see how an increase in the subperitoneal and omental fat bolster will increase intra-abdominal pressure and tend to raise the organs from within.¹ It is, therefore, a fundamental

¹ The same effect is produced by the enlargement of the uterus during pregnancy, and the improved well being of some asthenic women when in that condition is very readily explained on this basis.

principle in the management of asthenics to *improve the state of nutrition*

This is hardly the place to present in detail the technic of fattening cures. Let it suffice to bring out but a few "practical" suggestions. As a matter of fact, it makes relatively little difference what foods a patient takes for this purpose so long as he eats more. The amount of food eaten, as already pointed out, is very largely a matter of habit and in this case the habit of overeating should be cultivated as a virtue. Milk is the simplest and best fattener. If it is not relished cold, it may be taken hot, if not sweet, then fermented, if not plain, then as an eggnog, or mixed with butter or lactose, or cocoa, or coffee, or it may be peptonized or pancreatinized and taken as medicine. At least 1 quart of milk should be added daily to the ordinary diet during the first week of treatment. 2 quarts during the second. 3 during the third. A pint of cream, also can generally be taken during the day, distributed on cereals in coffee or with desserts. If the strict milk-bed-rest cure is prescribed even larger quantities can be taken without much difficulty. As an objective one should endeavor to reach the normal weight for the height, age and sex, as given in the standard insurance tables.

Finally, it need hardly be emphasized that surgical operations on neurotics in general and asthenics in particular should be avoided unless absolutely necessary. Operations for organic diseases are one thing, operations for colicky pains for ptosis, for the "drainage" of atonic organs for the removal of "potential sources of danger" of "nature's cesspools" or of "useless embryologic remnants" are quite another. A man may get over his neurosis, but he cannot get over his gastro-enterostomy or his short-circuited gut or his belly full of adhesions. At present we have many such unfortunates whose outlook is indeed gloomy. Fortunately thoughtful surgeons are daily restricting their operative indications more and more to definite organic lesions.

The following cases may be cited to illustrate some of the points developed in the foregoing presentation.

Case I Asthenia, Gastric Anacidity—Single woman, forty-two years old, dressmaker Came under observation August, 1920, complaining of diarrhea, weakness, steady loss of weight, and nervousness She has suffered from indigestion for the past twenty years The symptoms were variable, with free intervals Among the most prominent features were pains in the abdomen and back, distention, belching, regurgitation She required at least ten hours sleep nightly and made sure to get it, she would also lie down for a couple of hours during the day Latterly she had been having a particularly hard time and had cut down her food, article by article, in the hope of obtaining relief, until she was living largely on milk alone To this diet she attributed her present attack of diarrhea of seven weeks' duration

Examination revealed typical asthenic and ptotic habitus The patient was 30 pounds below her best weight (four years ago) and 40 pounds below the normal weight for her age and height Three test-meals showed a low total acidity and complete absence of HCl

Therapy Preliminary bed rest for one week (essential in the control of all diarrheas), bromid before meals, dilute HCl, 25 drops in a glassful of water, to be sipped during meals, bland, well-balanced diet, abdominal binder

Course Diarrhea stopped within two weeks, during which period patient gained 5 pounds In the next five months she gained 10 pounds more She still has some minor complaints, but has been able to resume work and is, on the whole, much better Corresponding to her physical progress there has been marked improvement in her mental attitude

Comment—A better result would undoubtedly have been secured in this case if the preliminary period of bed rest and forced feeding could have been lengthened by several weeks

Case II Nervous Vomiting—Irish maid, twenty-one years old, single Perfectly well until two years ago, when she began to have headaches and vomiting At first emesis would occur once daily, more recently, after each meal Patient feels quite comfortable for about an hour after eating, then nausea sets in,

and in about twenty minutes she vomits "all the food eaten" (This is a very common exaggeration) After vomiting she has soreness in the epigastrium for about half an hour No other symptoms Bowels move three times daily after meals Admits taking salts every morning since in this country—nine months—"in order not to get fat" A diagnosis of gastric ulcer had been made in this case

Examination showed a hypersensitive, apprehensive type of young woman Her color was florid, she was well nourished Indeed, she was 10 pounds overweight Physically she was normal This was considered enough evidence to dispose, for the time being at least, of the probability of organic disease She was given bromid before meals and a bland diet and told to discontinue her constant catharsis

One month later she reported that she had not vomited from the day treatment was commenced and was in every way in good health

Comment—Of course not every type of nervous vomiting is so easily controlled As an extreme contrast to the above might be mentioned a case of intractable vomiting with anorexia nervosa the patient dying after months of intense suffering A laparotomy by a careful surgeon failed to reveal any organic basis for the disorder

Case III Migraine; Habitual Constipation—Shop girl, twenty-five, divorced All her life has suffered from frequent bilious attacks migraine vomiting, prostration Spends several days each month in bed Always constipated, never spontaneous bowel movement full-blown cathartic habit as long as she can remember

Undersized, underweight, asthenic, hypersensitive Abdominal organs ptosed, abdominal wall thin and lax

In this case the therapy consisted of a firm abdominal binder, forced milk feeding no medication Two months later the patient was able to report that just as soon as she began to wear the binder the bowels commenced moving normally one, two, and even three times a day She has not missed a day from her work There has been one slight headache, but no vomit-

ing or prostration within this period. The patient "is the most surprised person in the world" at the result obtained.

Comment—Though not always so immediate and complete as in this case, the relief of migraine and constipation simply by abdominal support is by no means uncommon.

Case IV "Compulsion Neurosis", Diarrheal Syndrome—Young woman, twenty-five, school-teacher, private patient. Considerably distressed because, whereas ordinarily her bowels moved but once daily after breakfast, whenever she was excited, or particularly when worried about not being able to relieve herself—as at the theater, during examinations, etc.—she would experience a most compelling desire to go to stool. Under such circumstances the bowels might move two or three times in a short interval.

A thorough physical and laboratory study was negative. Treatment for five months with general care, sedatives, bismuth, was without any result other than occasional transient improvement. The patient then dropped out of sight for three years, to return with the following interesting report. For a long time she had been considerably worried over the presence of coarse hairs on her face. Before her first visit to me she had consulted a dermatologist who had advised her against local treatment. More recently she had consulted another skin specialist, who had removed the source of disfigurement and thus the hidden cause of her neurosis. Her bowel control is now much better, though she "can still work it up fine when she wants to think about it."

Case V Asthenia, Ptosis, Two Previous Operations for Constipation—Railroad brakeman, age twenty-eight, married. In the spring of 1917 began to suffer with pain in the lower right abdomen, constant, and radiating to the pit of the stomach. There were no colics, vomiting, or fever. Constipation was severe, the bowels often not moving for a week at a time. The condition was diagnosed by his doctor as "intestinal indigestion." Medical treatment for two months brought no relief. Operation was performed in June, 1917, for "chronic appendicitis." In four weeks there was return of all previous symptoms. Two

x-ray examinations were made, and the patient was told that he had "adhesions at the hepatic flexure and gas in the colon ' A second operation performed in June 1919, revealed a band strangling the small intestine Four weeks after the division of this band there was again recurrence of the original symptoms This time the patient was advised to have his colon removed However he hesitated at this proposition and came to us for opinion

Examination showed asthenic habitus malnutrition to the extent of 40 pounds under weight relief from support of the lower abdomen functional heart condition

A snug abdominal binder was prescribed, also mineral oil suprarenal substance and increased milk consumption Despite the fact that the patient continued at his arduous occupation, he improved from the start His bowels have been moving daily and he has gained 5 pounds At present (five months later) he is again troubled with gas and is restless at night He is still working, however, and still has his colon

CLINIC OF DR JESSE G M BULLOWA

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SCARLATINA

THE clinical picture of scarlet fever may best be kept in mind by considering the disease as developing in three stages. The validity of this grouping is witnessed by the fact that all the symptoms seem naturally to fall into their proper chronologic places. These three clinical stages are a *stage of swelling*, a *stage of shrinking*, and, finally, a *stage of septic complications*.

I shall not attempt to discuss the etiology of scarlet fever because there is no unanimity of opinion on this topic. It seems safe to believe that this disease—or, we may possibly say these diseases—are not induced by the ordinary streptococcus, because a streptococcus infection does not give the immunity which accrues from an attack of scarlet fever, and because the clinical picture of scarlet fever is not induced by the streptococcus when injected. This view does not conflict with the work of Miss Ruth Tunnicliff, who has found special streptococci frequently associated with scarlet fever.

It is difficult to realize that it is only one hundred and fifty years since Sydenham differentiated scarlet fever from measles while studying the epidemics which raged in London from 1760 to 1775. These diseases are quite different in their mode of onset. Scarlet fever is a veritable anarchist, blustering and waving a red flag. After a relatively brief incubation period lasting only a few days scarlet fever usually commences with any violent symptom that one may wish to conjure—a sudden high temperature, chills, vomiting, severe pains, convulsions, purging, delirium, and a severe sore throat. Contrast this with the gradual onset of measles with its cold in the head, pink

eyes, gradually rising temperature, and its prolonged incubation of more than two weeks

During the first stage of scarlet fever swelling is the keynote of the symptoms. This accounts for the high temperature, which may be explained by fixation of water and consequent absence of cooling, just as a motor heats which has insufficient water in the radiator. The temperature is frequently 103° F or it may reach 105° F or more. How different the sore throat of diphtheria, where the temperature is uniformly disproportionately low in comparison with the pulse and where it may be but slightly elevated. This absence of temperature in diphtheria is a menace which frequently delays the summoning of the physician. In scarlet fever the throat is swollen, the redness is not confined to the tonsils, but involves the entire soft palate and anterior pillars. There are dilated capillaries and a blotchy, sometimes hemorrhagic appearance. If the tonsils are ragged they are covered with a thick or filmy exudate. If the tonsils are covered by pillars and are swollen, they protrude into the pillars or escape between them. During this stage the crypts are filled with exudate and may give the patchy appearance of follicular tonsillitis. The inflammation in the throat is associated with enlargement of the regional lymph-nodes, which are tender, and, if the inflammation is severe, matted together. The inflammation of the lymph-nodes is expressive of the condition of the tonsils, if they are covered they will be compressed between the pillars and the pharyngeal muscles during swallowing movements, thus pumping toxins into the circulation. The tongue is red and the papillæ swollen. The diminution in the frequency of swallowing and masticatory movements because the remainder of the throat is swollen permits the epithelium to collect, resulting in a heavy fur.

The skin is swollen and red. The rash appears first about the neck, below the chin-ear line, and gradually progresses over the trunk, the face, and then to the upper extremities and lower extremities, where it is faint. It is apt to be more marked over the back from pressure on the bed, over the abdomen where the skin is thinner, and over the flexor surfaces of the extremities.

for the same reason. In the bend of the elbow there are characteristic reddish striæ which at times persist after the rash has faded.

The rash consists of a subcuticular flush on which is imprinted the essential and characteristic feature, the pinhead spots of special redness. This involves the entire surface and is explained by the fact that there are two sets of vessels serving the skin—the larger, deep subcutaneous vessels, and the finer network which penetrates the papillæ and perfuses the skin. The brunt of the disease seems to be expended on the vascular system, which is everywhere relaxed. Where the skin is very fibrous, as about the mouth, the rash is not manifest and we note the oft-mentioned circumoral pallor. The rash is especially well marked where the skin is thin, giving high color to the cheeks and about the eyes. The mucous membranes are also swollen and desquamate.

The rich supply of blood brought to the skin by dilated vessels interferes with the normal dehydration of the superficial epithelial layer, so that in their swollen state they close over the sweat follicles, the sweat follicles being especially well perfused are stimulated to extra function, and in this way the characteristic sudamina or water-blisters are formed, finally, the sudamina burst or they are opened by rubbing. The porous appearance of some desquamated areas is thus accounted for. The inflammatory reaction on the skin is so marked that the regional lymph-nodes are enlarged, usually in proportion to the amount of inflammation. The poison of scarlet fever seems to have an especial affinity for the chromaffin system throughout the body, the dilatation of the blood-vessels is so marked that there is a lowered blood-pressure.

Swelling of the viscera occurs. This is evidenced by the aching pains in the back which radiate in accordance with the segmental areas of Head. As a rule, the rash is intense in proportion to the severity of the disease. At times the capillaries break and the rash becomes hemorrhagic. Such cases are by no means fatal, but the prognosis is usually more grave. When the rash has been very severe, there is usually a prolonged

relaxation of the vessels, so that for weeks the skin has a yellowish hue, as after a burn or severe injury

During this stage of swelling occurs one of the most important conditions complicating scarlet fever. Because of the swollen pharynx, especially in the presence of adenoids and of blocked lymph-channels, the pharyngeal orifice of the eustachian tube may become occluded, so that the middle ear becomes inflamed. This complication may occur without warning on the temperature chart. The drum may be perforated or the irritating discharge may melt it away. It is the duty of the physician to prevent this unfortunate occurrence by careful daily watching with an otoscope and prompt incision of the drum. Sometimes a mastoiditis develops speedily and may require early operation. The absence of temperature rise is explained by the fact that there has been merely a surface extension of the disease process and no penetration to the interior of the body, with chemical digestive processes, water fixation, and consequent loss of cooling.

The temperature remains elevated for several days and gradually falls. The rash remains brilliant for three or four days and begins to fade. The throat and tonsils remain red for the same period, after which their swelling gradually subsides. The tongue, which until now has been coated and red, is completely desquamated with the returning appetite, and then by exposure of the large papillæ assumes the raspberry or strawberry appearance at its tip. At times the tongue is dry and glazed, but this is more frequent in mouth breathers.

By the fourth or fifth day in many cases the obvious symptoms of scarlet fever are very slight. In fact, at this time and until desquamation commences to appear, or by the tenth day, there is a period when the diagnosis of scarlet fever must be taken on faith in the history, for there may be very little visible evidence. This is the period which frequently leads to difficulty with the parents, who see no reason for continuing the isolation of children who are apparently well.

The *stage of shrinking* commences with the fall of temperature, which, as a rule, reaches normal on the fifth day. During

this period patients lose weight, notwithstanding that they may be fed an ample diet. The shrinking of the tissues and the contraction of the vessels leads to a diminished perfusion of the skin and to a stratification of the epithelium, due to the fact that there is a layer of tissue which has been overwell supplied



Fig. 165—Desquamation in scarlet fever

with water above a layer which is ill supplied. As a result the desquamation is not uniform, when the layer which received more moisture reaches the surface it will not be as dry as usual but will separate in coherent plaques from the underlying layer which contains less water and desiccates more rapidly. This

explains the desquamation in simple fashion. The desquamation is severe where the rash has been intense and prolonged, where the capillaries have had least support they will recover their tone latest, and consequently the desquamation will persist longest there—as between the fingers and toes (Figs 165, 166)

For several weeks the patients lose weight in spite of their bed rest and with an ample diet. When the tissues again resume



Fig 166—Desquamation in scarlet fever

their normal state of swelling, this swelling may exceed its original extent, so that frequently in uncomplicated cases the general nutrition seems improved after an attack of scarlet fever. This shrinking gives an explanation of the complications of scarlet fever, inclusively, they may be regarded as manifestations of the "septic" diseases. The streptococcus which enters the blood from the tonsil shows an especial affinity

for "pavement" epithelium, attacking the lining membranes of the heart, the blood-vessels in the kidney, the lining of the joints, and the flattened epithelium in the lung

There are two types of septic infections which complicate scarlet fever—those which occur during the stage of swelling and those which occur after the shrinking. The less frequent type is a sepsis which is continuous with the original invasion. The throat is invaded by a virulent organism and there is an associated enormous lymphadenopathy with infiltration of the tissues. The swelling of the tissues closes the orifices in the nose, with resultant sinus inflammation, causing profuse nasal discharge and sometimes ethmoiditis with exophthalmos.

These patients are overwhelmed with the toxin of the invading organisms which accompany the scarlet fever. The temperature does not fall. It may progressively rise. Such cases form the so-called septic type of scarlet fever. The condition of the patients is pitiable, the prognosis is very grave, but these are the cases which seem to be benefited by convalescent blood citrated, as used intramuscularly by Zingher in our hospital. The convalescent serum causes shrinking, probably by a precipitation of blood colloids, with liberation of water and consequent better cooling, for the fall of the temperature is frequently an encouraging omen.

When serum from convalescent patients is injected intradermally into a patient suffering with a scarlet fever the rash fades. The normal process of shrinking is initiated.

T. K. is a patient who was treated by Zingher with convalescent blood.

T. K., ten years of age, admitted January 16, 1921, third day profoundly ill. General erythematous, punctate rash, with marked hyperemia and injection of pharynx. Soft palate and tonsillar folds with dirty gray exudate covering left tonsil, less extensive membrane on right, buried covered tonsils, with large crypts, tonsils compressed on swallowing.

January 19, 1921. 120 cc convalescent blood, given into muscles, using deltoids, gluteals, and outer thigh regions and calves by Dr. Zingher. Taken from a patient seven days con-

valescent, six days ill At time of injection of convalescent blood the patient was delirious, temperature 106° F, pulse exceedingly small, almost imperceptible, during the night temperature reached 104° F and was 99° F the next morning General condition much better Still somewhat delirious No local reaction at site of injection

January 20, 1921 General condition much improved, pulse of better volume

January 21, 1921 Mental condition much better Pulse of good quality, 108, temperature 99° F

January 23, 1921 Right ear discharging

January 25, 1921 Tenderness over right mastoid Mastoidectomy was then performed

P P is another case which shows a brilliant result from the intramuscular use of whole blood by Zingher, a case in which the normal processes were either initiated or accelerated by the therapy

P P, one day ill, three and one-half years of age Prognosis doubtful Boiled lobster rash, throat congested, mild streptococcic exudate, tongue coated, clean beefy edges, moderate cervical adenitis

January 23, 1920 Convalescent (scarlet) blood from patient twelve days convalescent, who had been ill six days, given in deltoid region, thigh, leg, and buttock intramuscularly by Dr Zingher (Fig 167)

The patients seem to have a better chance if the pressure on the tonsils is relieved or the focus of infection in the throat is removed For them I have recommended incision of the phlca, or a tonsillectomy under local anesthesia It is not immaterial how the anesthesia is induced The needle should be introduced beyond the area of reaction, it should not penetrate the tonsil nor even the capsule The tonsil must be removed with its entire capsule, and if the tonsillar vein is thrombosed it should be included in the dissection This may best be done by employing Gatewood's technic

These patients must be sharply differentiated from those cases that die promptly after the invasion, with a high tem-

perature, a low blood-pressure and without much lymphatic

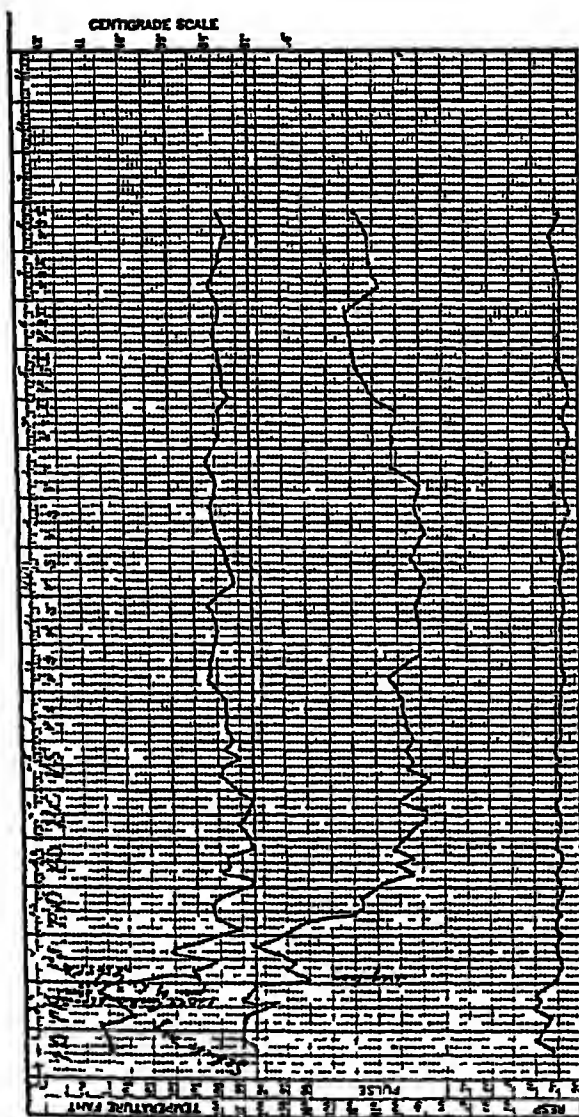


Fig 167—Case P

involvement. The latter have hardly any chance, though several very much prostrated patients have seemed to respond

to subcutaneous injections of adrenalin and to convalescent blood

The other and more frequent type of sepsis occurs after the temperature has been normal for a number of days or even for several weeks. In this type the general shrinking of the tissues removes the barriers which have walled off the focus of infection and there is an absorption of organisms from any focus in the body. Probably the traditional custom of forcing fluids during scarlet fever convalescence is an empiric effort to restore free water and thus prevent too great shrinkage. Though it is possible to restore the swelling state and thus restore the tissue interstices by giving fluid, and though the organism may not be liberated from a focus there may be an absorption of soluble bacterial toxins which are excreted through the kidneys and damage them. Infected teeth, infected tonsils—which are so formed or situated that when swollen they may be compressed between pillars and pharyngeal muscle upon swallowing—should always be removed in children. It is much better that sources of sepsis should be eliminated before the onset of scarlet fever, or early in its course before grave damage is done.

Processes may originate in the dislodgment of infarcts from the tonsillar vein, or they may occur from a secondary or even an unrelated focus. Such a case is the one I now report of a girl who developed a general fatal gonorrhea and peritonitis on the ninth day of her illness.

B W, a colored girl, fourteen years of age, had been six days ill when admitted, March 21, 1920. She had had a profuse vaginal discharge for several years.

Her temperature was normal, pulse 90, respirations 20. The pharynx was congested, the tongue quite red, and there was a punctate rash about the face, neck, and throat. Her pulse rose to 120 later in the day. Three days later her temperature had risen to 102° F, and on the following day there was extreme tenderness over the lower abdominal regions. Both sides were equally tender. There was no rigidity. Nausea and vomiting were present. She had suffered from pain in the flanks for the past several months.

The blood count was 34 000 The differentials showed Polynuclears, 90, eosinophils, 2, large lymphocytes, 7, small lymphocytes, 1

The vaginal smear showed many Gram-negative intracellular diplococci

That evening her temperature reached 105° F , pulse 158, and the following morning she died

One cannot lay too much stress upon the importance of septic foci and the part played by general tissue shrinkage in cutting down the barriers about them, thus permitting the entry into the body fluids of toxins or organisms It is this same mechanism that Theobald Smith pointed out as determining the fate of the tuberculous If the body tissues can digest the organism or toxin which is absorbed there may be a rise of temperature which is transient On the wards this is usually attributed by nurses and some doctors to constipation, the temperature falls and the bowels move simultaneously Constipation seems a definite explanation of the temperature in the majority of cases It does not, however, explain the possible enlargement of the nodes of the neck several days later (frequently with no rise of temperature) or the pains in some joint When the organisms have been arrested the local tissue response may be afebrile, while the primary general response may indicate no locus of attack

Enlarged lymph-nodes in the neck are the most frequent complication of scarlet fever They are usually the deep anterior chain and are painful and tender Frequently there is considerable perinodular infiltration out of all proportion to the softened area which ultimately results Frequently they resolve completely The nodes are best treated by applications of iodine or flaxseed poultices, and ample doses of the "tincture of time," unless there is definite softening, which should be drained only when the abscess points The nodes infected are usually deep in the neck and considerable mutilation through infiltrated tissue may be necessary to reach them These tissues withstand pressure from drains poorly The following case is illustrative

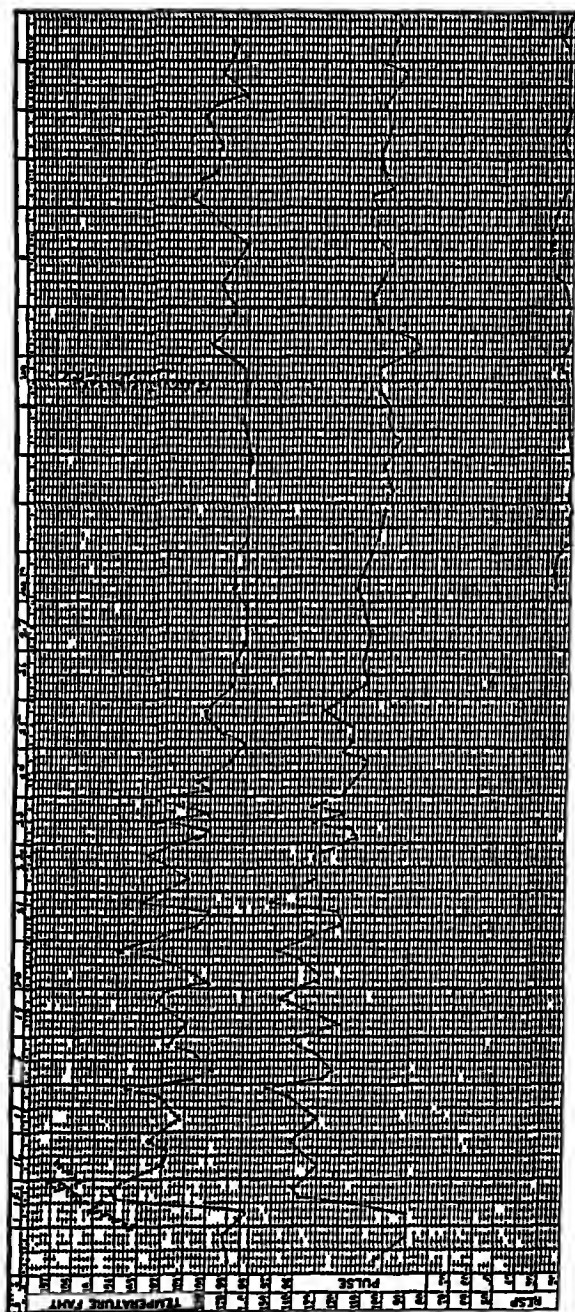


Fig 168 —Case J C Showing sudden onset with prolonged febrile period and complication after afebrile lasting a week

J C was admitted with chicken-pox on December 24, 1920. On January 15, 1921 he developed scarlet fever and we find the following note

January 15th Punctate rash on body and legs

Throat red and congested, tongue red on edges coated in middle Nasal discharge Large node on right side of neck Right ear draining left drum red no bulging



Fig 169—Large lymph nodes with much perinodular infiltration



Fig 170—Large lymph-nodes with much perinodular infiltration

After temperature was normal a week and child was apparently well, on February 1st bilateral cervical adenitis was marked (Figs 168-170)

February 8th Nodes are much smaller The temperature chart shows the sequence of events

The next most important complication is involvement of the joints It is a "rheumatism" which involves the wrists elbows, ankles or knees though sometimes the hip and shoul-

ders are involved, and still more frequently the fingers. There may be considerable peri-arthritis swelling, this is especially marked in those cases which are due to the gonococcus. Some ten years ago the writer collected 14 cases of joint involvement in children, in which the complement-fixation test for gonorrhea was strongly positive. Several of these cases are reported by Dr Mathias Nicol, Jr, in the Archives of Pediatrics. One of these cases was a male child, though many were children with a vaginitis. In some of them the blood-culture was positive, and



Fig 171 —Arthritis of left elbow

in some a septic rash which resembles chicken-pox vesicles initiated the attack. The gonococcus may be found in the blood without any mucous membrane discharge. Such a case is the one pictured.

It is very probable that otherwise innocuous guests were taken into the tissues as the result of the shrinking and were lodged in the joints. The gonococcus joints were treated with huge doses of vaccine and splinting. When induced by the streptococcus the inflamed joints are best treated by splint fixation and salicylates locally and by mouth. The streptococ-

cus joints have little swelling outside of the capsule and very



Fig 172 --Case J R

slight redness, contrasting strongly with the gonorrheal joints, which show much peri-articular puffiness In both varieties

the most important element is the elimination of the focus, whether in teeth, tonsil, or cervix.

J R is a mild case of scarlet fever which developed a severe arthritis which probably originated in the tonsils (Figs 171, 172)

J R, three and one-half years of age, was admitted January 20, 1921. He had been ill two days. There was a moderate general erythematous punctate rash, his throat was congested, there was no exudate, tonsils moderately large, not compressed by swallowing. Tongue coated, clean beefy edges.

February 1, 1921. Right otitis media—myringotomy.

February 3, 1921. Bilateral cervical adenitis, arthritis of left shoulder.

February 4, 1921. Arthritis of right elbow. Tonsils are completely covered by plicae and are compressed by swallowing. Tonsils have become much smaller.

Another case, G B, was a sailor, twenty-one years of age, who was admitted on August 30, 1919, with a temperature of 101.8° F, pulse 110, respiration 28. He had been two days ill with a diffuse erythematous rash, with slight circumoral pallor. The tongue was coated and the throat was slightly congested. His temperature reached normal on the seventh day, on the eleventh, twelfth, and thirteenth days it reached 101.2° F. Eight days later his left mastoid was operated upon, and subsequently the right mastoid. The tegmen antri was removed as well as the sinus plate, both being necrosed and soft. The sinus and dura were apparently healthy. After another eight days there was pain in the left sacro-iliac joint, referred to the gluteal region and down the thigh. The inguinal region was painful and tender. There were enlarged nodes. The motion of the left thigh and leg was limited, causing pain in the left inguinal region.

His blood count showed 26,000 white cells. The discharge from the wound in the left ear was thick and yellow, showing many extracellular diplococci, staphylococci, and a few short-chain streptococci.

There was subsequent involvement of both shoulders, elbows,

knees, and fingers, with a low febrile course, the temperature occasionally reaching 102° F. The patient's tonsils had been removed, but the foci from his teeth were neglected and the carious teeth were permitted to remain.

He encumbered a bed in the hospital for five months and finally was transferred to his home in California, where a daring surgeon opened his septic, though quiescent, hip-joint liberating toxins from which he perished in a few days. How much better it would have been if the septic foci in his teeth had been properly eradicated before the onset of his scarlet fever or early in its course.

That the various complications are due to invasions from a common focus is witnessed by the frequent association of several different complications in the same individual. Frequently we find involvement of the heart, lungs, kidneys, and joints, either seriatim or at the same time.

M. A. is a patient who shows the invasion of different organs, the occurrence of multiple complications, and the effect on the temperature chart (Fig. 173).

M. A. was six years of age and had been ill eleven days on admission, January 7, 1921. His condition was such that the prognosis was doubtful. Fading rash on abdomen. Pharynx congested, tonsils enlarged, no exudate. Strawberry tongue. Bilateral cervical variety. Right ear draining. Bronchitis.

January 15, 1921. Left otitis media. Myringotomy. Right mastoiditis. Antitoxin rash.

January 23, 1921. Bilateral cervical adenitis.

January 25, 1921. Arthritis of fingers.

January 29, 1921. Arthritis of hands and feet.

February 2, 1921. Arthritis of hands and wrists.

February 7, 1921. Arthritis of elbows, knees, and ankles.

The next most frequent complication of scarlet fever is probably nephritis. A true nephritis should be sharply distinguished from a nephrosis which accompanies almost all infectious diseases at the outset. A true scarlatinal nephritis occurs three weeks later. If the blood-pressure has been observed, its sudden rise may be an inauspicious sign. The patients

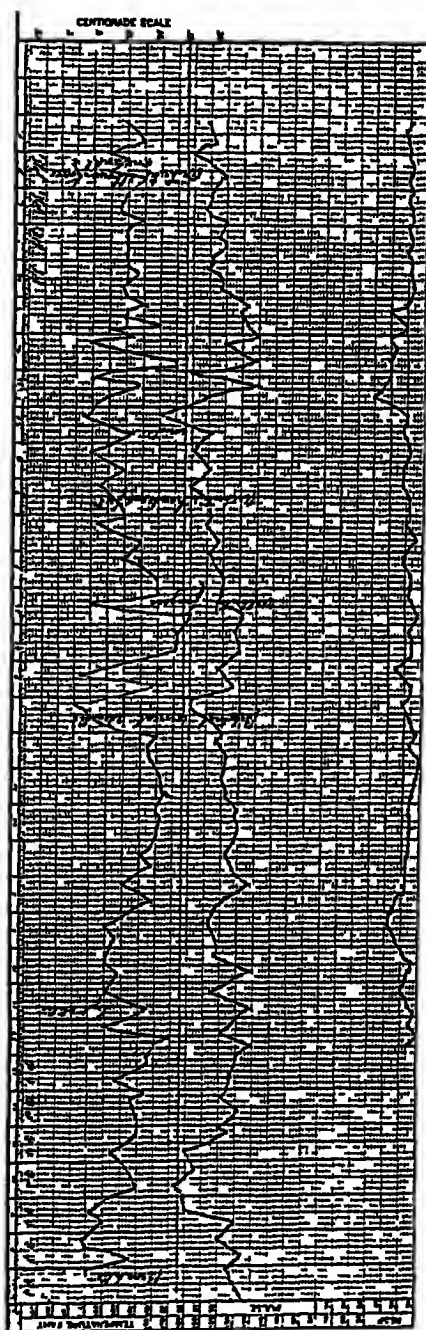


Fig 173—Case M A

become puffy and swell up gradually. This seems to be nature's way of limiting further absorption of toxins, for the kidneys can no longer excrete the salt or water. There may be casts and albumin, and red blood-cells occur in proportion to the extent of renal involvement. However, the urine picture is no measure of the severity or of the permanent damage which will result from this invasion. The kidneys may be uniformly involved or they may be involved in discrete patches. The swelling of the body is not a measure of the ultimate damage. Only prolonged observation of the blood-pressure and tests revealing kidney inadequacy show what has been destroyed. The site of election is the glomerulus.

In those cases where there is proliferation of Bowman's capsules the capillary loops are compressed and the prognosis for long life is grave. Time alone can determine in any individual case whether these proliferative changes have been initiated. If hyaline degeneration of the glomeruli loops develops, only one or two of the five loops in every glomerulus may be involved, and the others may lengthen and become tortuous and substitute for those destroyed. In such a case recovery is apparently complete.

We are convinced that limitation of salt and of fluids rests the inflamed kidneys, and we prefer this method to the sweating of patients in order to eliminate edema and the attempt to flush kidneys which will not work. Moreover, the limitation of salt and water concentrates the body fluids so that the emulsion state is partly broken and elimination of water results. In this way the same effect is obtained as by injection of Fischer's solution. A Karel diet should be instituted.

The damage to the kidneys is not accomplished at once, but there may be repeated invasions or a continuously operating destruction. In two children with a true nephritis, where the tonsils were removed for other reasons, the clinical symptoms of nephritis subsided, and from my experience it seems reasonable to attack the focus rather than the damaged kidney. Little children bear water deprivation ill and frequently their kidney involvement baffles therapeutic endeavor. Convulsions may be

treated with luminal At times lumbar puncture may be indicated When they are controlled in this way and the edema subsides I have not seen the convulsions recur

The lungs are frequently involved in scarlet fever, and pneumonia carries off many patients either as an early or late complication At times empyema may occur B S is such a case The accompanying chart illustrates how evil is the omen of a continued high temperature

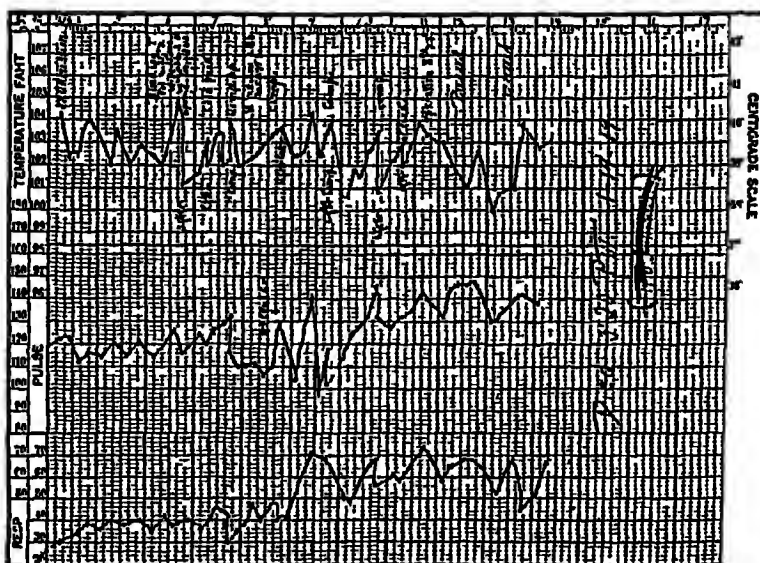


Fig 174—Case B S

B S, seven years of age, who had been ill two days, was admitted January 4, 1919 She had an intense punctate rash all over her body A general adenitis Oral mucosa ulcerated Tonsils enlarged congested, covered with film of exudate Tongue coated strawberry type at tip and on edges Hyperpyrexia Pulse rapid, low tension

On January 5th her throat was congested, no exudate

Lungs Right lung, marked dullness of midlobe anterior and posterior, and in axilla region Breath sounds diminished anterior, diminished in axillary region

Heart Sounds fair quality rapid

Pneumonia consolidation of whole right lung with pleurisy

January 11th Aspiration at angle of scapula on right side, pus obtained

Another case is the following

H M four years of age, had been ill three days on admission, January 29 1921 Exudate on both tonsils, croupy cough, 10 000 units antitoxin given

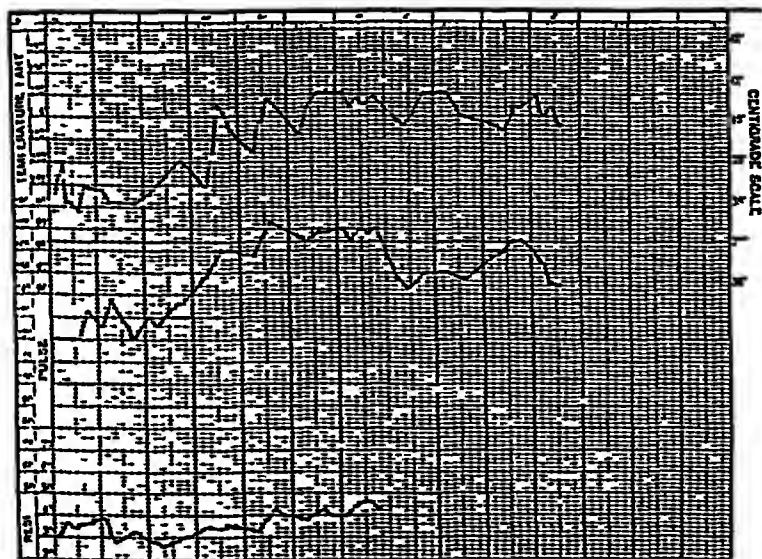


Fig 175—Case H M

February 1st Scarlatiniform rash on body bilateral cervical adenitis nasal discharge, croupy cough

February 5th Large moist râles over right apex anteriorly, bronchial breathing over same area Heart negative Nasal discharge still present

In some cases pneumonia may possibly be due to the swelling of the bronchioles early in the course of the disease obstructing normal lung drainage The temperature in these cases continues high from the beginning Such a case is the one reported which we had opportunity of observing from the outset,

as it developed while the patient was in the hospital with diphtheria

I have already mentioned otitis media and the subsequent mastoid complications and have shown an illustrative case

Treatment—In the discussion of scarlet fever thus far we have not mentioned its treatment, though we have laid stress upon the treatment of some complications. The patient should be kept at rest in bed. In a number of cases we have found adrenalin valuable in combating initial vascular paralysis. I have already mentioned the value of Zingher's method of initiating the normal shrinking processes by the intramuscular use of citrated whole blood. In view of the swollen skin and the fact that the body has much fluid to lose, it is important that the skin should be kept in good condition, and at the Willard Parker Hospital patients receive a daily warm bath. They are kept on a diet of milk for several weeks and then given bread, fruit, and cereals.

Nasal discharges are treated by gentle irrigations. No attempt is made to disinfect the passages.

For thirty days patients are quarantined. Then they are released if there is no evidence of mucous membrane discharge. Frequently a nasal or ear discharge persists, even subsequent to a mastoid operation. The removal of tonsils and adenoids terminates this discharge, though sometimes there is a brief exacerbation, a result of the traumatic swelling.

CLINIC OF DR DAVID PRESWICK BARR

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DYSPNEA AND HYPERPNEA

Two Cases Representing Two Types of Abnormal Respiration, Full Discussion of Both Types

For the past year you have been engaged in the study of physiology and have learned much concerning the functions of the normal body. From this time your attention will be focused upon the body in disease and you will learn of the symptoms arising from disturbance of one or more of the normal functions. The diseased body must not be considered a thing apart. The same principles which apply to the normal may be applied to the abnormal, and your entire experience in medicine should be illuminated by the use of physiologic principles in the study of disease. The interrelation of physiologic and pathologic function may be illustrated by a consideration of disturbances of respiration.

Today there are presented to you two patients, both of whom exhibit abnormal respiration. The first is suffering from incompetency of the heart, the second is a case of diabetes with acidosis. If the patients are carefully observed, it will be seen that they differ in many ways. The respirations of the cardiac are shallow and rapid. The patient is bolstered up in a bed the head of which is elevated. We find upon questioning him that he cannot lie down without intolerable distress. He is breathing with effort and is suffering from dyspnea (difficult respiration) and orthopnea (inability to breathe in the supine position). The diabetic on the other hand, lies flat in bed.

While his respirations are a trifle rapid and extremely deep he does not seem to be suffering any great discomfort. He exhibits the objective sign of hyperpnea (increased breathing). Except for the abnormal respiration these patients seem to have little in common. It is probable that the causes and the mechanism of the disturbed breathing are as different as the appearance of the patients themselves.

Before entering upon the discussion of the causes of these pathologic forms of respiration it may be well to review briefly the physiologic facts which are essential for their proper appreciation. We may consider three aspects: the task of respiration, the mechanisms by which the lungs accomplish it, and the means by which respiration is regulated to perform the work imposed by the body.

The task of respiration is twofold: it must supply sufficient oxygen to support the necessary combustion processes of the body and it must remove carbon dioxide, the end-product of oxidation. In the following discussion we shall neglect the oxygen function and shall confine our attention to the problem of the proper elimination of carbon dioxide. If, during rest in bed, an individual produces 300 c c of carbon dioxide per minute the respiration must be regulated to eliminate that amount. When, during severe exercise, the carbon dioxide production rises to 1500 c c per minute, the respiratory mechanism must be equally capable.

By what means do the lungs accomplish this elimination? In normal individuals the air in the deeper portions of the lungs is in approximate equilibrium with the blood in the pulmonary capillaries. A free exchange of carbon dioxide through the capillary walls is possible and the partial pressure of carbon dioxide on the two sides is almost the same. A certain portion of each expiration is composed of air rich in carbon dioxide, which may be considered, for the purposes of elimination, the effective air. The total expiration, however, is a mixture of this air with the so-called dead space which fills mouth, throat, trachea, and large bronchi, and which is of the composition of the atmosphere. The percentage of carbon dioxide in the total

expiration must be the resultant of the mixture of these two portions, ordinarily 35 to 4 per cent. In normal individuals at rest the ordinary expiration (tidal air) averages about 500 c c. The dead space varies but averages about 130 c c. Thus, in such a normal individual the effective portion of each expiration has a volume of 370 c c. The relative volumes of dead space and effective air are of great importance in determining the amount of carbon dioxide eliminated. In very shallow expirations, of 200 c c or less, the volume expired may be little more than is necessary to clear the dead space. In spite of the multiplication of such shallow expiratory efforts the amount of carbon dioxide eliminated may be very small.

The depth of respiration depends in large part upon the volume of the lungs. This may be divided functionally into two portions, the residual air which remains in the lungs after the deepest expiration, and the vital capacity which is defined as the volume of the maximum expiration after the greatest possible inspiration. Vital capacity can be measured and it is found to vary roughly with the size of the body, perhaps rather closely with the surface area. In a man 5 feet, 11 inches in height and weighing 150 pounds it amounts to about 4000 c c. When this is compared with the 500 c c, which is the average tidal air, one appreciates what an enormous factor of safety exists in normal lungs. It must be remembered however that the vital capacity represents the maximum respiratory effort. No one could maintain this maximum respiration over any long period. Dr F. G. Peabody¹ has shown that when normal men are subjected to severe exercise the tidal air may arise to one-third of the vital capacity. An individual with a vital capacity of 4000 c c might under stress increase his tidal air to 1500 or 1600 c c. When the maximum tidal air has been attained any further demands upon the respiration must be met by increase in rate.

In order that the lungs may answer satisfactorily the requirements of the body the following conditions must obtain. There must be a free interchange of carbon dioxide between lung capillaries and the air in the lungs. The effective air must

constitute a relatively large portion of the total expiration. The lung volume must be sufficient to allow great changes in the depth of respiration.

Finally, we may consider how it is that the respirations can be so delicately regulated as to meet exactly the demands of the body. You have learned in physiology that the respiration is governed by the respiratory center in the medulla and that the activity of this center is dependent upon the reaction of the blood. You have learned that the degree of alkalinity of the blood is practically a constant, and that it is maintained under the most varying conditions of environment. Any tendency toward an increase of the blood's alkalinity causes a depression, any decrease, a stimulation of the respiratory center.

It has been shown by Dr. Lawrence Henderson² and others that the reaction of the blood depends upon the behavior of carbon dioxide. This may be present in the blood in two forms, as carbonic acid and as bicarbonate. The amount of carbonic acid is a direct function of the partial pressure of carbon dioxide, increasing with any increase in carbon dioxide pressure. The amount of bicarbonate depends upon the available alkali or, as it is usually called, the alkaline reserve. This is best defined as the alkali (sodium, potassium, etc.) which is available for combination with carbon dioxide under the conditions existing in the body. When the carbonic acid is to the bicarbonate as 1 is to 20, the reaction of the blood is approximately normal.

$$\frac{\text{Carbonic acid}}{\text{Bicarbonate}} = \frac{1}{20} = \text{Normal reaction of the blood}$$

It is apparent that this ratio may be disturbed and the respiratory center stimulated in either one of two ways. If carbon dioxide accumulates in the body, the partial pressure of carbon dioxide is increased and the amount of carbonic acid is increased out of proportion to the bicarbonate. If, on the other hand, the alkaline reserve is diminished for any reason, the bicarbonate is decreased in amount without corresponding

change in the carbonic acid. Since carbon dioxide is being continually produced in the body the first mechanism is always present and furnishes the normal stimulus of respiration. As long as the lungs function normally and the carbon dioxide production is not excessive the reaction of the blood is not greatly disturbed. Change in the reaction of the blood by decrease in bicarbonate may occur to some extent in normal individuals, but is oftener the expression of pathologic change.

We are now in a position to consider with greater profit the pathologic respiration of the patients before us. Let us first examine the cardiac. He is a man thirty-seven years of age. We find by inquiring into his past life that he had an attack of acute rheumatic fever at the age of twelve and that he has had two subsequent attacks, one at the age of fifteen and the last at thirty. Between these illnesses he has had frequent attacks of sore throat, some of which have confined him to his bed. After the second attack of acute rheumatic fever the patient was told that his heart was affected. He noted no ill effects, however, until about two years ago when he felt slight distress in breathing upon climbing stairs. This gradually increased until he found that even when quiet he was conscious of a certain difficulty in breathing. At the same time he developed a hacking cough and several times he noted that his sputum was streaked with blood. At night he could no longer lie flat in bed and found his only comfort in the use of several pillows. These manifestations of disease increased until his shortness of breath and cough forced him to seek medical relief in the hospital. Upon examining his heart it was found that his mitral valves were insufficient and stenosed, that his heart was enlarged. There was a large accumulation of fluid in the right pleural cavity.

In the stenosis of the mitral valves the chief strain naturally falls upon the left auricle. A backing up of blood into the pulmonary circuit results and a condition known as congestion occurs. Great changes in the function of the lungs accompany this congestion. The capillaries become distended and changes take place in the alveolar walls. We may suppose, although

we do not know it, that the elasticity of the lungs is diminished and that perhaps the thickness of the alveolar walls is increased. There often accompanies the condition a pleural effusion, such as we have seen in this patient. All of these factors tend to diminish lung volume.

As a matter of fact, it is found that this patient, who is of the height and weight of our supposed normal man, has a vital capacity of only 1500 c c instead of the 4000 c c which he probably possessed before his circulatory function failed. If we consider that the maximum tidal air is one-third of the vital capacity, we find that under the greatest stress of exertion he will be able to expire only 500 c c with each breath. This is the tidal air of a normal man at rest. The tidal air of this patient has been measured and found to be 300 c c. If we subtract a dead space of 130 c c we find that the effective air of each respiration is only 180 c c.

The decompensated cardiac is limited in another way. In normal individuals the expired air may be said to contain about 3.5 to 4 per cent of carbon dioxide. In the cardiac before us the carbon dioxide in the expiration is only 2 per cent. This, of course, might be attributed to the greater proportion of dead space air in each expiration, but upon further examination we find another reason. If a sample of air be taken from the deeper parts of the lungs it is found to contain only 4.5 per cent carbon dioxide instead of the 5.5 per cent of the average normal person. In other decompensated cardiacs³ we have found carbon dioxide in effective air as low as 2.5 per cent. In normal individuals the partial pressure of carbon dioxide on the two sides of the capillary walls is approximately the same. In decompensated cardiac patients the pressure of carbon dioxide in the effective air is very low while that in the blood is normal or somewhat increased.

It is apparent that the lungs of this decompensated cardiac patient are very poor instruments for the elimination of carbon dioxide. The exchange between pulmonary capillaries and the air in the lungs is imperfect. The effective air constitutes a relatively small portion of each expiration, and the lung volume

is so limited as to allow only the slightest increase in depth of respiration. Since each portion of the air contains less carbon dioxide the volume of breathing must be increased. This can be accomplished only by a more rapid rate. The patient before you has a minute volume of 10,800 cc to deliver which he must breathe thirty-six times.

In addition to his imperfect lung function the decompensated cardiac labors under another disadvantage. His carbon dioxide production is increased. Working in this clinic Dr. Peabody and Dr. DuBois¹ found that the basal metabolism of the dyspneic cardiac is high in some cases 50 per cent above the normal level. Since this is the condition at rest, one sees how impossible it is for the cardiac to care for any increase in carbon dioxide production; how intolerable his respiratory distress must become with even slight exercise.

In cardiac dyspnea we have an example of the first mechanism by which the respiratory center may be stimulated. The difficulty in the elimination of carbon dioxide causes a constant tendency toward the accumulation of carbonic acid in the blood. This is not accompanied by a corresponding increase in the alkaline reserve. The tendency toward increase of the $\frac{\text{carbonic acid}}{\text{bicarbonate}}$ ratio is always present and the pulmonary mechanism is continually stimulated to an increased ventilation which it is ill fitted to accomplish.

The diabetic is a young man only twenty years of age. He was in excellent health until about six months ago when he noticed that he was unusually thirsty, that he had a voracious appetite, and that he was passing large amounts of urine. At the same time he noted that he was losing weight and that his strength which had been considerable, was failing. He consulted a physician, who discovered sugar in his urine and put him on a diet low in carbohydrate. With this diet there was some improvement in his condition and the boy, thinking that he was fast recovering, treated himself to a more liberal diet. It was then that the catastrophe occurred. He became very ill. When he was brought to the hospital he was in a semi-

stupor, his tongue was glazed and red, there was a fruity odor upon his breath, and he was exhibiting in an exaggerated manner the breathing which you now observe. You will note that he is not orthopneic, that his respiration is rather rapid, but that its chief characteristic is abnormal depth. He seems to be reaching for air, a type of breathing which is often called "air-hunger."

In diabetes there is probably no fault in the pulmonary mechanism. Increase in carbon dioxide production can be easily compensated by an increase in ventilation. Any stimulation of the respiratory center will meet with ready response in the lungs. We find that in diabetes the level of metabolism is normal or slightly increased. At rest, the diabetic produces no more carbon dioxide than does a normal man, and yet in the patient before you there is obviously a tremendous increase in ventilation.

You have already learned in physiology that diabetes is often associated with an imperfect oxidation of fat. Beta-oxylbutyric acid, which is ordinarily a stage in the oxidation, may not be burned and so may accumulate in the body. Since beta-oxylbutyric acid is a stronger acid than carbonic, some of the alkali that has been in the form of bicarbonate unites with the new acid to form oxylbutyrate, with a resultant change in the $\frac{\text{carbonic acid}}{\text{bicarbonate}}$ ratio. In normal individuals we have seen that

$$\frac{\text{Carbonic acid}}{\text{Bicarbonate}} = \frac{1}{20} = \text{Normal reaction of the blood}$$

When bicarbonate is broken down by the new acid, the ratio is disturbed, the alkaline reserve is diminished, carbon dioxide is liberated, and more carbonic acid is formed. The respiratory center is tremendously stimulated and respiration becomes more rapid and deeper. Carbon dioxide is eliminated with the greatest rapidity and the elimination will continue until the reaction of the blood returns to normal. The body must maintain its normal alkalinity and we often see diabetics

with a greatly depleted alkaline reserve, with a carbon dioxide pressure and a concentration of carbonic acid only half the normal, but with a normal reaction. The lungs are stimulated to pump out carbon dioxide until the $\frac{\text{carbonic acid}}{\text{bicarbonate}}$ ratio returns to its necessary $\frac{1}{20}$, but the actual values of carbonic acid and of bicarbonate are at a lower level. This is the cause of the great air-hunger seen in the state of diabetic acidosis.

The reduction in the carbon dioxide pressure of the blood is reflected in the percentage of carbon dioxide in the effective air of the lungs. In diabetic acidosis the air in the deeper portions of the lungs may contain only 2.5 to 3 per cent carbon dioxide. As in the cardiac, this means that each volume of air expired contains less carbon dioxide. To accomplish a normal elimination the ventilation must be kept at a higher level. The carbonic acid and hence the percentage of carbon dioxide will remain low until the depleted store of alkali has been replenished. In diabetics we may see an increased ventilation long after the first acute symptoms of air hunger have passed.

These cases represent two types of abnormal respiration. In both the respiratory center is stimulated by a disturbance of the $\frac{\text{carbonic acid}}{\text{bicarbonate}}$ ratio. The causes of disturbance, however, are entirely different and the symptoms arising from them are not alike. It would be very satisfactory if we could divide all abnormal breathing according to these two types and could say that all conditions in which dyspnea is a symptom are analogous to that of the decompensated cardiac, that all hyperpneas are like the hyperpnea of which diabetic acidosis furnishes an example. This is not possible. Abnormal respiration is an expression of disturbed function in the body, but whether this disturbance is in the respiratory center in the blood, or in the lungs themselves must be determined in each separate disease. In heart conditions and in diabetes our knowledge has become quite extensive. Thanks to the very excellent work of Dr. R. W. Scott,⁵ we now know some of the factors in the dyspnea of emphysema. The picture is not that

of cardiac dyspnea We know something concerning the abnormal respiration of tuberculosis and of pneumonia, comparatively little of that in nephritis Much work upon the application of physiologic principles to the study of these diseases must be done before our knowledge of dyspnea and hyperpnea is complete, and yet it is only through a full understanding of the factors involved and of the functions disturbed that we may hope to treat these conditions rationally

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CLINIC OF DR ARTHUR L HOLLAND

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THE SIGNIFICANCE OF SOME GASTRO-INTESTINAL SYMPTOMS

In the normal gastro-intestinal canal the digestive secretions are put out quantitatively and qualitatively within limits that are most elastic compared to those of products of glands not connected with digestion. The size of the individual, his habits, the character of his food, his emotions, and many other factors may exert modifying influences on this output. In disease there would seem to be no limit to the variations in quantity, quality, and time of secretion.

Gastric analysis has fallen into disrepute largely because too much was claimed for it in the beginning, and laboratory reports of gastric analyses, even to this day, are considered too literally, the interpreters not being familiar with some of the underlying principles governing the digestive processes.

Of all the influences that can possibly modify both the quantity and quality of the gastric juice, gastric or intestinal motility is perhaps the most potent and constant. Given a motility that is normal throughout the canal except where constitutional disease is present or other extragastric modifying influences are exerted, a stomach will put forth a secretion within normal limits for the individual both as to quality and quantity. But with a motility that is embarrassed or accelerated the secretion of gastric juice will change in character and quantity. Increased gastric motility with rapid emptying from whatever cause will tend to decrease the quantity, the acidity, and the enzyme content of the juice. A deficient motility with delayed emptying has the reverse effect in proportion to the degree of the delay. When the motility is not seriously interfered with, or even increased, but with a reflex pylorospasm in

operation at times when the stomach is empty, a continuous secretion results. These conditions frequently obtain in the reflex pylorospasm from extragastric irritation.

A hypersecretion with or without hyperchlorhydria results from an irritable pylorus with spasm which is operative during the stay of chyme within the stomach. This happens in ulcer at or near the pylorus.

In benign, partial stenosis of the pylorus there is not only some retention, but an increased secretion and increased acid values as well. In a malignant stenosis we may have some increase in secretion, and where all of the gastric cells have not been atrophied because of the constitutional disease and the accompanying gastritis, an increase in acid as well as a possibility.

In malignant disease of the body of the stomach there is usually rapid emptying. This alone would tend to diminish the acid even were it not for the inhibiting effect of the constitutional disease on the gastric cells. But in early carcinoma of the pylorus with obstruction, when the constitutional disease has not caused entire destruction of the cells, a normal or even an increased acid is frequently found. In ulcer of the body of the stomach, the motility not being affected to any great extent, the acid values are usually normal, or, in a fair percentage of cases, may be low. In gastritis the acid values are usually determined by the type or tone of the organ. Or, in other words, the motility here has the same effect relatively as in the normal stomach or in other diseases. A cowhorn-shaped stomach, that drains quickly even though the mucosa be only moderately atrophied, will produce a gastric juice much lower in acid and less in quantity than a hook-shaped organ with slightly impaired motility in which the cells are badly damaged. The few cells that remain normal in the latter case are stimulated to increased activity because of slow emptying.

Considering these simple principles of gastric secretion, it can be readily seen how difficult a diagnosis becomes when too much reliance is placed upon gastric analysis. On the other hand, armed with a knowledge of the motility as it can only be obtained through the employment of the fractional test-meal

and the fluoroscope, the interpretation of these findings becomes not only a fascinating pursuit, but a long way toward a scientific solution of the diagnostic problems involved

Most of the distress that is experienced by those suffering from functional or organic diseases of the stomach or intestines is brought about through irregularities in the motor mechanism of the canal, and the secretory disturbances are largely caused by deficiencies or excesses of the motor function

It has been proved, for example, that the pain in gastric or duodenal ulcer is not the result of high acid, but rather of increased tension in the walls of the stomach or duodenum, which, in its turn, is caused by an increased peristalsis working against either a spasm or an organic obstruction at or beyond the pylorus, that high acid is only a result of this motor disturbance. This can be demonstrated by giving a patient suffering from duodenal ulcer a mixed barium and carbohydrate meal, and by means of fractional extractions of the stomach contents carried on simultaneously with fluoroscopic observations, the onset of the distress can be seen to coincide not with the peak of the acid curve, but with the time when the pars-pylorica are in the most pronounced spasm, this occurs usually as the last part of the meal is being propelled through the pylorus and for some time after the stomach is empty. Additional food introduced into the stomach relaxes these parts and the intragastric tension subsides, relieving the pain. Alkalies overcome spasm in the same mechanical manner as does food, although it is not unlikely that an altered reaction also relieves spasm.

It is quite well established that the pain of ulcer is not caused by the raw surface of the lesion coming in contact with the highly acid contents. There are probably as many people who regularly take soda for the relief of gastric distress whose gastric juice is low in acid as there are those whose acid is high. It is the relief of peristaltic unrest, spasm, or other motor disturbance which the food and soda give, even where there is total lack of acid.

Pain farther along in the tract is likewise caused by inequalities in the tension of the walls of the canal due to spasm.

or obstruction of one kind or another. The pain here is sharp and colicky because there is a limit to the compensatory stretching of the intestinal wall, while the walls of the stomach are so built that increased tension can be taken care of. Colicky pains are, therefore, never intragastric in origin except rarely, where severe spasm temporarily isolates an antrum from the rest of the stomach and the tension is here suddenly increased. But even under these conditions the cramp is not as sharp as that of intestinal origin, it is better described as an intermittent grinding pain.

The pyrosis common to many gastric disturbances is undoubtedly caused by hyperesthesia of the gastric mucosa. Here hyperchlorhydria, or gastric contents high in organic acids, may be operative, but persistent soreness or ache is usually caused by an inflammatory process extending through to and involving the serous layer of the stomach or pylorus. It frequently happens that epigastric pain is caused by lesions remote to this region. It is possible that such pain may be reflected, but it more often occurs as the result of a pylorospasm reflexly excited.

Take, for example, the ileopyloric reflex. The working of this reflex can be easily demonstrated by means of the fluoroscope. It is a delicately adjusted reflex which acts as a semaphore between the ileocecal valve and the pylorus. When the contents of the ileum reach the ileocecal valve the pylorus is automatically closed, and it remains closed until the pressure in the ileum is relieved by the passage of the contents into the cecum. In those cases in which the ileocecal valve is damaged or affected by inflammatory or other changes in the adjacent tissue, such as appendicitis, adhesions, or malposition of the parts, this reflex would seem to run amuck and a more or less persistent pylorospasm results. Under these conditions it is not difficult to understand the reason for epigastric pain and the resulting hypersecretion or continuous secretion in chronic appendicitis and other lower right quadrant disease.

It cannot be so easily demonstrated, but that there is a reverse reflex from the pylorus to the ileocecal region is a probability. The epigastric pain and occasionally the increase of

distress in the lower right quadrant immediately on the taking of food would in such cases suggest this possibility

The behavior of the stomach shadows, observed fluoroscopically, in gall-bladder disease is in many cases characteristic and would suggest that there is some reflex connection between the gastric motor mechanism and the gall-bladder. It is, of course, possible that this effect may be caused directly by an extension of the inflammation to the pars-pylorica. But the peristaltic activity in these cases is not confined to this part of the stomach alone. Here we see the entire stomach overactive, the peristaltic waves deep, and of the type seen in obstruction. It can be demonstrated, however, that there is no real obstruction that the opaque meal passes with undue rapidity into the small intestine. This coincides with the acid values, for in most of these gall-bladder cases the acid tends to be subnormal, and continuous secretion is for this reason in these cases rare. Occasionally we do see spasm of the antrum or of the pylorus in gall-bladder disease. Here, as in chronic appendicitis, we can trace the reason for the gastric distress and the secretory irregularities. Not infrequently in spastic constipation the stomach behaves in a similar manner.

Any inflammatory process in the abdomen may affect the gastric motility one way or another—kidney stone, for instance, chronic pelvic inflammation, malposition of the uterus, or its appendages, the early stages of pregnancy. Those extra-abdominal diseases that most frequently reflexly affect the gastric function are fibroid phthisis and beginning cardiac decompensation. The functional cardiac diseases, the arrhythmias, for instance, do not affect the gastric function directly. The indigestion here probably results from the faulty nerve control which also causes or accompanies the cardiac disturbance. A decompensated heart causes congestion in the liver and congestion of the vessels in the gastric walls and so acts indirectly on both secretion and motility.

Reverse peristalsis does not often take place in those portions of the gastro-intestinal tube that are of relatively large caliber—the stomach and colon—the exceptions are in the act

of vomiting in pyloric obstruction and where there is organic obstruction in the large bowel. In the esophagus it is fairly common even where there is no definite lesion, a slight cardio-spasm is sufficient to excite the act—hence the regurgitations in the neuroses. The duodenum is also prone to behave in this manner on slight provocation. In fact, the small intestine is more sensitive to motor impulses than other parts of the tract, and when its motility is embarrassed even though slightly, a reverse peristalsis seems to be its method for relieving the resulting increased tension and pressure. Obstruction low down in the small intestine and in the colon may result in the vomiting of intestinal contents, as the fecal vomiting of intestinal obstruction proves. The passing back of this material into the stomach is possible only through a reverse peristalsis, it cannot be proved that some reverse peristalsis is not a part of the normal intestinal digestive processes, making for a thorough emulsification of the chyle and giving it more opportunity for absorption. The occurrence of bile in the vomitus at the end of protracted vomiting attacks does not necessarily signify a reverse peristalsis in the duodenum. The pressure exerted by the abdominal muscles acting against a fixed diaphragm is sufficient to squeeze bile into the stomach, but where bile is found in gastric contents that have been aspirated or have been vomited early in an attack a reverse peristalsis is likely operative. Adhesions about the first portion of the small intestine and kinks here are of frequent occurrence, and cause symptoms through reverse peristalsis that are at times puzzling.

There is one interesting syndrome of frequent occurrence that has until recently been misinterpreted. The layman calls it "an old-fashioned bilious attack," and many doctors fall back on "auto-intoxication" as a diagnosis. They both treat it successfully by means of cathartics—usually calomel. They are content in the thought that a "torpid liver has once again been pounded back into activity." They point to the enormous quantity of bile vomited as proof of the diagnosis and the almost instant relief of the lassitude, headache, furred tongue, etc., when the bowels have been cleaned out, as evidence that "accu-

mulated poisons had done it all" As a matter of fact, the problem here is usually a mechanical one, but rather involved and complicated The first step is an overloaded colon due to lack of exercise, overeating or other hygienic errors Then because of irritation at the ileocecal valve—probably through back pressure—a reflex pylorospasm is set in operation through the ileopyloric reflex, and it is not long before sour eructations and the spilling over of the clear, sour fluid of hypersecretion marks the second step And then, reflexly, from the irritation in the lower bowel—perhaps the weight of the colonic load is responsible—reflex peristaltic unrest of the stomach is made manifest in nausea This culminates in a more pronounced peristaltic activity and retching and vomiting are established The immediate temporary relief experienced after vomiting is no doubt due to the sudden lowering of the tone in the abdomen through the vomiting releasing in this manner, temporarily at least the pull or irritation at the source This cycle is repeated until by enemas or cathartics the offending material is removed from the colon It may be that in these cases through backtracking of colonic contents into the ileum because of a distorted, inefficient ileocecal valve, that some absorption takes place, thus explaining the icteric conjunctivæ and fetid breath The quick relief of the headache and the sense of buoyancy and well-being that follow the colonic cleansing suggest very strongly the removal of mechanical irritation—a chestnut burr has been removed from beneath the saddle of a bucking horse A colon that becomes unduly heavy or which for some reason or other, suddenly loses its tone and sinks low, can through a pulling down of the mesentery cause an acute angulation of the duodenum at the junction of the descending and transverse portions The symptoms that result are strikingly similar to those of the "periodic bilious attack" The distention of the first and second portions of the duodenum and a tendency to reverse peristalsis in these portions can be demonstrated fluoroscopically in such cases The periodicity is dependent upon the colon gradually accumulating weighty contents or for some reason such as prolonged fatigue or psychic reaction losing its tone and thus

changing its position. The complete and usually permanent relief from such attacks which follow the proper support of the abdomen, combined with correct hygiene in which physical training of the patient has a large part, is rather strong evidence that this explanation is not far wrong. One must, of course, not forget migraine. There is no question but that there are many cases of genuine migraine with a similar symptom complex, but the percentage of these dwindles very materially when the fluoroscope and other modern methods are employed in differentiating.

The practice of belching is indulged in by many people who suffer from functional or organic gastric disease. It is important only as an indication of the temperamental status of the individual. That it is a frequent symptom in gall-bladder disease does not lend to this symptom any undue significance. A neurotic woman may become an addict soon after the first appearance of some trifling gastric disturbance, while a less nervous patient will only discover its potentiality after years of nagging abdominal distress. Peristaltic unrest of the stomach is the immediate cause of the establishing of the habit. The upper part of the stomach normally contains a collection of air that has been swallowed with the food. When peristaltic activity is unduly stimulated, either through emotional causes or reflexes from adjacent or distant organs in trouble, in an effort to relieve the resulting increase in tension, some of this normally imprisoned air is forced into the esophagus and gently rifts up. This slight lowering of tension is at once appreciated by the individual and he soon learns the *modus operandi* of the finished act. He is not conscious of the fact that at some period in the belching cycle he sucks in air, either directly from the larynx or through the nasopharynx. This sucked-in air does not always reach the stomach, but in some cases distends the esophagus enormously, to be expelled at once to the satisfaction of the patient and consternation of those about him. It has been recently stated that reverse peristalsis in the stomach is the cause of this symptom. I have made many thousand fluoroscopic observations, and only three or four times in my experience have I

witnessed the phenomena of reverse peristalsis in the stomach, and in these cases an aborted act of vomiting was probably responsible for the appearance

In a diverticulum of the esophagus, cardiospasm, or an organic esophageal stricture the regurgitation of tasteless, unchanged food particles is of diagnostic import. Otherwise it is only a manifestation of a reverse peristalsis in the esophagus and significant only as a symptom of a neurosis—an acquired trick of an accomplished belcher.

The sensation of nausea may be immediately caused by either an increased or erratic peristalsis or an absence of motor activity. Usually it occurs in the latter state. It is most often present when the tone or tension in the stomach is suddenly lowered or altered. Psychic reaction, hunger, pain, or reflexes of intra- or extragastric origin may excite the condition. Alterations in the output of the secretory apparatus are secondary to nausea, seldom the cause of it.

In the act of vomiting we have the commonest example of a reverse peristalsis. The act is usually a combination of a voluntary and involuntary reflex activity. It may, however, be and frequently is entirely involuntary. That it may occur as a symptom in nearly every possible disease, or like tears, give expression to any of the emotions, does not rob this symptom of its diagnostic importance. But it is of value only when carefully studied in its relation to other symptoms and to the body functions.

It will not be possible at this time to discuss the vomiting of reflex origin. But we will briefly consider the act of vomiting as a symptom in organic disease of the stomach. The vomiting or, more properly, regurgitation that is a feature in organic obstruction of the esophagus or a diverticulum is of unchanged food, considerable mucus may be admixed, and in malignant obstruction "prune juice" or frank blood may be added. This vomiting or regurgitation occurs frequently at night or when the patient assumes the prone position. When vomiting occurs frequently and the vomitus is small in amount, it is as a rule, not caused by obstruction of any kind, but rather by non-

obstructing, inflammatory changes in the gastric mucosa. Except for blood and occasionally the characteristic odor, the vomitus in gastric carcinoma when such a growth is not an obstructing agent, and that of gastritis cannot be differentiated—in fact, the vomiting in carcinoma is largely due to the gastritis which is secondary to the malignant process. Pain may precipitate the vomiting in gastric carcinoma, but this vomiting rarely relieves the pain unless the growth is an obstructing one, in fact, vomiting frequently increases the distress. The vomiting in ulcer of the body of the stomach usually occurs at the height of the pain. It relieves this pain by relieving the intra-gastric tension. There is nothing characteristic about this vomitus except perhaps the relatively high acid and blood when bleeding is a feature. The vomiting due to prepyloric, pyloric, or postpyloric ulcer may be either of the retention type or the irritation type. When in ulcer it is due to obstruction we, of course, have all the characteristics of a retention vomitus—mucus and food that has been retained longer than normal. Where there is a partial obstruction with a moderate delay in the emptying of the organ we may get the hypersecretion type of vomitus. This is made up largely of gastric juice. It means that the gastric secretory apparatus has been overstimulated, it is working not only during the digestion of meals, but when the stomach is empty as well. This type of vomitus, however, is more frequent where only pylorospasm is present, as in the reflex pylorospasm of a chronic appendicitis. This latter form of vomiting occurs usually when the individual leans over, as in tying a shoe, it is more of a spilling over than an actual act of vomiting. The vomiting caused by obstruction frequently occurs at night. This is because the intragastric tension is increased at the end of gastric digestion and is, therefore, high several hours after the heavy evening meal. And gravity also may have something to do with it, particularly in those stomachs that have been decompensated, the prone position favoring the emptying of the organ. This is also true of those stomachs not organically obstructed, but which are enormously dilated through lack of tone and low position.

CLINIC OF DR. MURRAY H. BASS

MOUNT SINAI HOSPITAL

ORTHOSTATIC ALBUMINURIA, WITH SPECIAL REFERENCE TO ITS TREATMENT BY A SPINAL BRACE

CASE REPORT

ALICE R, born October 4, 1909, was first seen by me October 22, 1912. She was a first child, born by forceps delivery. She was breast fed for three months, and was well up to the age of two years when she had an attack of bronchopneumonia from which she made a good recovery. Since that time she had been in good health and was brought for general physical examination.

Examination October 29, 1912 revealed a normal child, weight 38 pounds 10 ounces. No abnormality whatever. Urine showed no albumin or sugar.

The child was not seen for a year when she again came for examination. During the period which had elapsed since her last visit she had been perfectly well. At this time November, 1914, her weight was 42 pounds. Her physical examination was negative. Her urine showed a large amount of albumin, but no cells or casts.

January 1915. Morning urine was normal, afternoon specimen showed ++ albumin.

The child was not seen by me until March, 1918. At this time aged eight and one-half years she weighed 54 pounds and was 52 inches in height. Her morning specimen of urine showed no albumin the afternoon specimen showed ++. Microscopic examination was negative. Examination of her spine now revealed a distinct lordosis of the lumbar region (Fig 179). Corrective exercises and calisthenic drilling was given by a special instructor with little change either in the spinal deformity or in the urinary findings.

It was therefore decided in December, 1918 to let the child wear a spinal brace. This brace has been worn continuously to date and has resulted in greatly lessening the quantity of albumin excreted.

This case is interesting because it brings up for discussion the question of albuminuria in children, and especially that type of albuminuria known as orthostatic. Until relatively recently such cases were supposed to belong to the curiosities of medicine, but as more attention was paid to urinalysis the condition was found to be by no means an uncommon one. The reason that so many of these cases were overlooked was, first, because the urine was not examined, and second, because if examined and found free from albumin, it was never re-examined. Investigation has shown that if the urine of children attending dispensaries be examined frequently, a surprisingly large number of children will be found to be suffering from albuminuria, and, moreover, if investigation be carried still farther, it will be found that the albumin is usually present only in the urine passed after the child has been up and about, the morning specimen remaining free from albumin. In collecting statistics of these interesting cases Langstein found that of the children over five years of age attending his clinic in Berlin 12 per cent were sufferers from orthostatic albuminuria. However, there are all degrees of albuminuria, and one must not expect to find the urine boiling almost solid in every case, as it did in the case above detailed. Many of the urines show merely a trace of albumin in the afternoon specimen, whereas the morning specimen is quite normal. None of the specimens, however, show the presence of casts.

A number of different factors probably enter into the etiology of this condition, but the most important apparently is a postural defect of the spinal column, causing an exaggerated lumbar lordosis. The connection between lordosis and albuminuria was first pointed out by Jehle, who in a brilliant study showed that many of the cases could undoubtedly be explained on purely mechanical grounds. Apparently the child's faulty attitude causes some sort of pressure on the renal vessels, with a result-

ing congestion of the kidney and a consequent passage of albumin into the urine

The lordotic factor, moreover, harmonizes well with the previous conception of a particular "orthostatic type of child" (Erich Frank and Martius), for it has long ago been pointed out that orthostatic albuminuria was particularly common in thin, rapidly grown children. The reason for the occurrence of the albuminuria in these children is, therefore, probably not due to the "type" of child, but due to the fact that such narrow-chested frail children are precisely the ones prone to spinal curvatures. The albuminuria is not an expression of the frailty of the child, but of its abnormal spinal curvature.

However, we cannot emphasize too strongly the fact that the habitus of the child is of great assistance in making the diagnosis of orthostatic albuminuria, for the lordosis may be so slight as to be overlooked unless especially sought for.

It may be well briefly to review the characteristics of the type of child that so frequently suffers from orthostatic albuminuria. The child is usually between ten and fourteen years of age, it has grown rapidly, appears frail and "lanky." It is usually pale, due to some vasomotor disturbance, though its lips are very red and the hemoglobin percentage normal. The hands are very often very much cyanosed, especially in cold weather, and sweat easily. The combination of the bright red lips, the pale skin, and the blue hands is quite striking. The thorax is narrow and long, with a narrow intercostal angle, while the scapulæ protrude prominently like wings. The abdomen is often unduly prominent, so that when the child is seen in profile the typical enteroptotic habitus is revealed. The lordosis of the lumbar spine may or may not be prominent. These children are, moreover, highstrung and irritable, they cry readily and are easily alarmed.

Figure 176 well illustrates the build of this particular type of child. The photograph is that of a little girl eleven years of age who was referred to the Pediatric Service of Mount Sinai Hospital as a case of nephritis. Her chief complaints were dizziness and failure to gain in weight. The only abnormalities

on examination were enlarged tonsils, the spinal deformity, and the albuminuria. The urine when excreted during the upright position always showed the presence of albumin, whereas that excreted while the child was recumbent was constantly albumin free. No casts were found.



Fig 176—Child suffering from orthostatic albuminuria. Note enteroptotic habitus, prominent abdomen, "winged" scapulae, and lumbar lordosis. (From Pediatric Service of Mount Sinai Hospital, courtesy of Dr Henry Heiman.)

The subjective symptoms complained of in such cases are chiefly headache, cardiac palpitation, precordial pain, dyspnea on exertion, faintness, and hypersusceptibility to cold. As all of these are clearly referable to disturbances in the cardiovascular system, it is natural that the heart and arteries should have commanded especial investigation, and, in truth, much interesting investigation has been reported on this subject. The dyspnea and palpitation together with the albuminuria at once gave rise to the supposition that these were cases of weak heart, an hypothesis which was, moreover, apparently corroborated by the findings obtained by percussing the area of cardiac dulness. Owing to the narrow chest and to the overaction of the heart investigators were led to the erroneous conclusion

that the heart was hypertrophied or dilated. We therefore find the terms "*Wachstumshypertrophie*" (growth hypertrophy), "*dilatation de la croissance*" (dilatation due to growth) "dilatative weakness," and similar descriptive epithets applied to the heart

in these cases. However, careful studies made with the fluoroscope have definitely shown that the heart in such cases is not only not enlarged, but, on the contrary, is often particularly small or narrow¹. Apparently the finding of the drop heart or narrow heart in a considerable percentage of these children adds further proof to the fact that we are dealing with a somewhat subnormal individual, since the drop-shaped heart may be looked upon as one of the stigmata characterizing the asthenic habitus.

Not only the heart but the blood-pressure has been the subject of much study in these cases. In a large group of children investigated in regard to blood-pressure we were unable to draw any definite conclusions, there being no characteristic change in the recumbent or the upright posture². Recently others (Mason and Erickson) have shown that in cases of orthostatic albuminuria the albumin varies with the diminution of the pulse pressure. Their cases revealed a very marked drop in the size of the pulse pressure due to a rise in diastolic pressure, as soon as the upright posture was maintained. We have been unable to corroborate this finding in one case in which we have tried to do so. One fact has been definitely shown, however, and that is that these cases, unlike nephritics, do not suffer from high blood-pressure.

The renal function in cases of orthostatic albuminuria, as measured by the phenolsulphonephthalein test, is normal when the children are at rest in bed (Hempelmann). However, when such children are placed in exaggerated lordosis, causing marked albuminuria, the phthalein excretion drops considerably.

From the above brief exposition we may say that many of the children showing orthostatic albuminuria may be grouped in the class of asthenic individuals and that their urinary anomaly is related to this only indirectly through its dependence on the accompanying spinal curvature.

The diagnosis of orthostatic albuminuria is made when we

¹ "Heart Size and Heart Function in Children Showing Orthostatic Albuminuria. An Orthodiagraphic Study," M. H. Bass and H. Wessler, *Archives of Int. Med.*, April, 1913.

² Bass and Wessler, *Archives of Int. Med.*, January, 1914.

find albumin in the urine secreted while the child is in the upright posture, and none present while the child is recumbent. Moreover, casts must be constantly absent. The importance of this last condition lies in the fact that there is a variety of true nephritis in which albumin accompanied by casts appears only after the assumption of the upright position.

Having decided that a child is a subject of orthostatic albuminuria, the question at once arises as to the prognosis. The well-informed layman is, of course, aware of the fact that the presence of albumin in the urine is of serious import and will immediately desire information as to the significance of its presence, and as to the relation the albuminuria may bear to permanent kidney injury. I believe that in answer to these queries it is correct to reassure the parents, since the prognosis is in general good, most of the cases undergoing spontaneous cure at puberty or during early adolescence. Moreover, it is well to know that though autopsied cases revealed complete absence of gross or microscopic lesions, nevertheless the continued passage of large quantities of albumin may conceivably in itself finally give rise to irritative changes in the kidney structure.

This brings us to the treatment of this condition, and it is here that great strides have been made by the discovery of the close relationship between albuminuria and postural defect of the spine. First and foremost we must emphasize the fact that it is useless, nay it is wrong, to deprive these children of exercise. Here, again, the character of the complaints, all of them referable to the cardiovascular system, have misled physicians into treating these cases as cases of cardiac weakness. While we agree that, owing to their generally frail constitution, these children ought not to overexercise to the point of exhaustion, we believe that light exercise, such as calisthenics, mild bicycle riding, and general outdoor playing, should be encouraged. We consider this important for the reason that since much of the albumin is dependent on the spinal curvature, and since this in turn may be modified by strengthening of the muscles, exercise which tends to develop weakened muscles must indirectly bene-

fit the albuminuria The following is of interest in this connection

Anna L., aged fourteen years, first seen January, 1914

Family History—Patient is the youngest of four children An older sister died of acute nephritis at the age of twenty years, six months ago

Past History—Measles at six years Not subject to sore throat

Present Illness—For the past year the child has complained of backache, headache, and severe palpitation on exertion Six months ago the urine was examined on account of the death of the sister, and a large amount of albumin was found The diagnosis of nephritis was made and the child was put on a very rigid non-protein diet She was removed from school, was sent to the country, and was forced to spend most of her time resting She had been constantly under this régime until she came for examination

Physical Findings—Well-built girl with slight lordosis Weight 104 pounds Hands cold and clammy and cyanotic The basic second heart sounds exaggerated No signs of cardiac enlargement Systolic blood-pressure 125 Physical examination otherwise negative

Urine—Clear, amber, specific gravity 1015, acid albumin ++ Microscopic examination showed a few epithelial cells After lying prone for twenty minutes, the test for albumin revealed only a faint trace (This diminution in the albumin on assuming the recumbent position was subsequently repeatedly shown to be present)

It is evident that we are dealing here with a typical case of orthostatic albuminuria which had been incorrectly diagnosed, and which was being subjected to a treatment not in the least calculated to improve it The subsequent progress of this case will be referred to later on

Before we attempt to treat a child suffering from orthostatic albuminuria we should inform the parents that the condition is essentially a chronic one and that though the albumin can be diminished by proper treatment, the case is by no means "cured",

since as soon as treatment is suspended the albumin has a tendency to return. After a period (years in most cases) the albuminuria will in most cases subside. Our treatment is of use because it stops the excretion of albumin and thus perhaps prevents needless damage to the tissues of the kidney.

The child should be put under good hygienic conditions and any foci of infection such as diseased teeth should be removed. The diet should be a general one, no restriction on protein being necessary. Definite exercises tending toward the strengthening

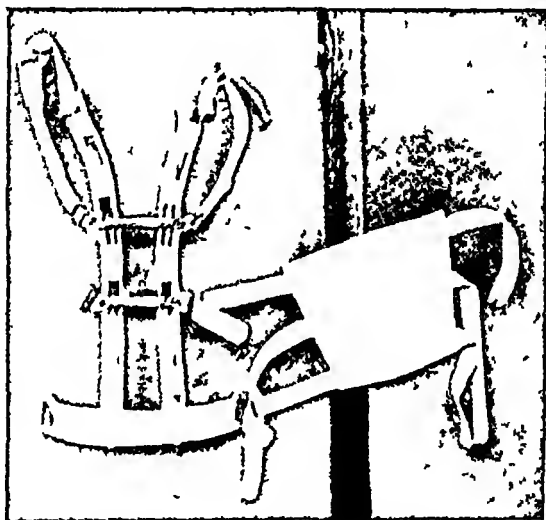


Fig. 177 —Spinal brace used to reduce the lumbar lordosis

of the lumbar muscles should be prescribed. The child is told to lie on its back and is made to draw up its knees so as to approximate them toward the axillæ, thus producing a marked temporary kyphosis in the lumbar spine. This movement is to be repeated ten to twenty times every morning and evening. Ordinary calsthenic exercises should be ordered and plenty of outdoor playing. In other words, the child should not be treated as sick.

For the correction of the spinal curvature a brace should be worn. The accompanying illustration (Fig. 177) shows the type

which I have found very satisfactory. The brace consists of two rigid upright bars which extend from the shoulder to the waist, parallel to the spinal column, and are supported on a girdle. The posterior half of this girdle is rigid; the anterior portion consists of straps and a flat canvas abdominal support.



Figs 178-180—Fig 178 shows brace being worn. Fig 179, Profile view showing lumbar lordosis. Fig 180 shows reduction of lordosis while wearing brace.

Figure 178 shows the brace being worn. The brace should be applied on arising in the morning, and kept on until the child is ready to go to bed. Immediately upon removing it at night and before applying it in the morning, the above described exercise should be performed.

The value of the brace is well shown in Figs 179 and 180,

the former a profile view of Case I without the brace, the latter the same with brace in place. The correction of the lordotic curve is quite evident.

The progress of a case under treatment is well illustrated by the course of Case II, whose history was given above.

January 6, 1914. A. M. urine negative for albumin. P. M. urine ++.

February 16, 1914. Patient has been exercising and taking iron and strychnin. A. M. urine negative, P. M. urine ++.

April 8, 1914. A. M. urine negative, P. M. urine ++, complains of severe backache.

May 2, 1914. Has finally consented to wear a brace. A. M. urine negative. While wearing brace urine shows a trace of albumin. Standing, with brace removed, results in appearance of albumin.

June 1, 1914. No more backache. With brace urine shows a heavy trace of albumin.

June 27, 1914. Only a faint trace of albumin present.

July 2, 1914. Without brace urine shows a very heavy trace of albumin. After wearing brace (two hours) urine shows a very faint trace.

December 5, 1914. Feels well. A. M. urine negative for albumin. Noon urine negative (with brace). Without brace urine shows a very faint trace.

January 16, 1915. Left off brace for four days. Urine shows + albumin. This convinced the patient of the necessity of continuing treatment, and she wore the brace one and a half years more, when she was able to discard it for good.

February 23, 1918. Patient perfectly well. Now eighteen years of age. Weight 142 pounds. Urine negative even after prolonged standing.

From this case history we may note that the albuminuria was at once affected by the treatment, but that it required two and one-half years of constant wearing of the brace before the albuminuria entirely disappeared. It is interesting, moreover, to note the coincident disappearance of the subjective symptoms of malaise and backache with correction of the spinal

deformity This is all the more remarkable because the lordosis was very slight and would probably have entirely escaped observation had it not been for the albuminuria which led to special attention being paid to the spine

The improvement in the child's general condition apart from the improvement in the urine coincides well with experience of Talbot and Brown¹ These authors published a series of cases where, by correcting postural defects, symptoms apparently quite unrelated to the child's posture were relieved Thus constipation, indigestion, and attacks of so-called cyclic vomiting were cured by the application of a spinal brace Although these investigators barely mention albuminuria, from our own experience we can add, as shown above, that this too is greatly benefited by correcting the postural defect

Case I, whose history is given above, well shows how very promptly the albuminuria will diminish as soon as the spinal deformity is corrected (Fig 179) Immediately after wearing the brace this child's urine instead of boiling almost solid, revealed but a trace of albumin For the past twenty-two months, during which the brace has been worn, the urine has never shown more than a heavy trace of albumin, though repeatedly examined During this time the child has been given a full normal diet and has been permitted to exercise, including dancing and calisthenics, all of which she is able to enjoy without being inconvenienced by wearing the brace

It has been my practice to continue the use of the brace until leaving it off for a day or two no longer results in the reappearance of the albumin If the albuminuria immediately recurs, the use of the brace must be continued As we mentioned above the correction of the postural defect serves a twofold purpose—first, it stops the albuminuria, which in itself may have a “sparing” effect upon the kidney, and second, it certainly improves the child's general condition and helps to relieve the lassitude and general weakness so often complained of by the type of child revealing orthostatic albuminuria

¹ Amer Jour Dis Child, September, 1920

CLINIC OF DR N ROSENTHAL

MOUNT SINAI HOSPITAL¹

SOME ATYPICAL CASES OF LEUKEMIA

In order to understand the classification of the leukemias and render a diagnosis in obscure cases a few examples of which will be given today, one must be thoroughly acquainted with the various types of mature and premature white blood-cells. The ideas in regard to these cells have undergone repeated changes, so that the names of the cells have changed from time to time. On account of the relatively large number of cases of leukemia admitted to the Mount Sinai Hospital I have had an excellent opportunity of investigating the various cell types occurring in this disease, and of studying the clinical and pathologic data. For the privilege of examining these cases I am indebted to the Physicians of the Hospital.

The following facts presented are the result of this study. The results obtained with the oxidase reaction in the various leukemias have been the subject of a previous communication.

The classification of the leukemias depends upon the type of the predominant cell present in the blood and upon the course of the disease—acute or chronic. The acute forms of leukemia are associated with a predominance of the premature white blood-cells and the chronic forms are associated with an increase of the more mature cells, while transitional forms are usually present in both. In his studies on the oxidase reaction on leukemic and normal blood the author called attention to a classification of the white blood-cells into the following main groups—myeloid, lymphoid, and monocytic—and to a classification of the leukemias into three groups corresponding to the

¹ Based on demonstrations given during ward rounds of Dr N E Brill and Dr E Libman.

predominant cell type Table I offers a comprehensive idea of the various mature and premature cells found in these groups Leukemias are also classified as leukemic and aleukemic The latter term is used by the author to indicate a slightly increased, normal or subnormal white cell count associated with an absolute and often a relative increase of a certain group of mature or premature white blood-cells—aleukemic myelosis for an increase of premature myeloid cells and aleukemic lymphadenosis for a relative and often absolute increase of lymphoid cells (Barker) The term "leukopenic leukemia" (myelemia or lymphemia), suggested by Libman and Ottenberg, is used to much better advantage, as the term "aleukemic" seems to be ambiguous Transitions from the leukemic to the aleukemic group or vice versa may occur

TABLE I
CLASSIFICATION OF LEUKEMIAS

Group	Type of predominant cell	Granules	Course	Oxidase reaction
I Myeloid	1 Myelocytes	A None B Auer bodies C Few azure granules	Acute	A Negative B Positive (con- fined to Auer bodies) C Positive only in cells containing granules
	2 Myeloblasts	A None B Azure C Premature Neutrophilic	Acute	A Negative B Positive C Positive
	3 Myelocytes	A Neutrophilic B Eosinophilic C Basophilic	Chronic	A Positive B Positive C Negative
II Lymphoid	1 Small lymphocytes	None or azure	Chronic	Negative
	2 Small lymphocytes and atypical lymphoblasts (Sternberg's leukemia, lymphosarcoma)	None or azure	Acute Chronic Subacute	Negative
	3 Large lymphocytes	None or azure	Acute (rare) Chronic	Negative
	4 Plasma cells	None	Very rare	Negative
III Monocytic	1 Myeloblastic type	None or azure	Acute	Negative, except in myeloblasts
	2 Lymphoid type	None or azure	Acute	Negative
	3 Endothelial type	None or azure	Chronic	Positive (granules darker)

Before we proceed with the presentation of the cases it seems to be advisable to say a few words concerning the technic em-

ployed in the identification of the cells and also to discuss briefly some of the cells mentioned

For the study of morphology thin smears in ordinary leukemias and somewhat thicker ones for aleukemic cases are made on clean slides Pappenheim's Jenner-Giemsa method is used One must experiment these days with the two stains in order to obtain the best results We are using at present an American Jenner and a French Giemsa (R A L product) in the following manner Jenner—one minute, dilute with distilled water—one minute, wash in distilled water and stain with diluted Giemsa (1 drop to 2 c c distilled water)—twelve minutes

The oxidase reaction, although of less importance than morphology studied with a good polychrome stain, can be done by using alpha-naphthol and dimethylparaphenyldiamin (indophenol blue synthesis due to presence of oxidases in the cytoplasm) or the benzidine-polychrome method of McJunkin (peroxidase reaction) The indophenol reaction is done as follows

1 Fix smear preferably with 1 per cent osmic acid—fifteen seconds

2 Wash in running water—five minutes

3 Alpha-naphthol	1 0	} two minutes
Absolute alcohol	30 0	
Distilled water,	100 0	
Conc ammonia,	0 3	

4 Follow with 1 per cent solution of paraphenyldiamin—two minutes

5 Counterstain with aq pyronin (1 per cent)—thirty seconds

6 Blot

Such slides can be examined with an oil-immersion lens

The Leukocytes of Normal Blood (Table II)—In normal blood there are three series of cells which were well described by Ehrlich With the exception of the azure granules of the lymphocytes first described by Michaelis and Wolff and of the irritation cells of Turk there have been very few new findings in normal blood since Ehrlich's publications The division of the normal leukocytes into three groups by Pappenheim Aschoff,

and others is of great importance in the study of the leukemias, which, as already pointed out, can be divided into three main types corresponding to such a classification.

TABLE II
CLASSIFICATION OF NORMAL BLOOD-CELLS

Series	Type of cell	Per cent.	Absolute number
I Myeloid	A Polymorphonuclear neutrophils	65-70	4000-6000
	B Polymorphonuclear eosinophils	2-4	150-300
	C Polymorphonuclear basophils	0-0.5	0-50
II Lymphoid	A Small lymphocytes	20-30	1500-2000
	B Large lymphocytes	5-10	
	C Plasma cells	Rare	
III Monocytic	A Large mononuclears	0.5-2	200-600
	B Transitionals	2-6	

The Leukocytes of the Myeloid Leukemias —A study of the cells in chronic myelogenous leukemia, especially in cases which have over 500,000 white cells, reveals transitional stages from the myelogone to the myelocyte. The characteristics of these cells are well summarized in Table III.

TABLE III
PREMATURE MYELOID CELLS

Cell	Nucleus	Nucleoli	Cytoplasm	Granules	Oxidase reaction
Myelogone	Round, oval or slightly indented Reticulated	Two to six or large central	Small rim	None Auer bodies Few azure (cytoplasmic or diffuse)	Negative Positive (confined to Auer bodies or granules)
Myeloblast	Round, oval or indented Reticulated	None or few	Small or moderate	None Azure Premature neutrophilic (Cytoplasmic or diffuse)	Positive or negative
Myelocyte	Round, oval or irregular	None	Small or moderate	1 Neutrophilic 2 Eosinophilic 3 Basophilic	Positive Positive Negative

As an example of the various cells found in chronic myelogenous leukemia the following blood count is interesting

Hemoglobin	67 per cent (Kuttner)	
Erythrocytes	3,144,000	
Leukocytes	136,000	
Differential		
Cells counted	500	
	Per cent.	Absolute number
Polynuclear neutrophils	67.2	92,393
Polynuclear eosinophils	0.2	272
Polynuclear basophils	0.8	1,088
Myelocytes, neutrophilic	19.6	26,656
Myelocytes, eosinophilic	0.4	544
Myelocytes, basophilic	0.2	272
Myeloblasts	8.2	11,152
Myelocytes	2.0	2,720
Megakaryocytes	0.2	272
Lymphocytes	0.8	1,088
Monocytes	0.4	544
Normoblasts	1 per 500 white blood-cells	
Megaloblasts	1 per 500 white blood-cells	

The myelocyte is a predominant cell found in some acute leukemias and in the terminal stage of some chronic myelogenous leukemias. Klein considers it to be the stem cell of the

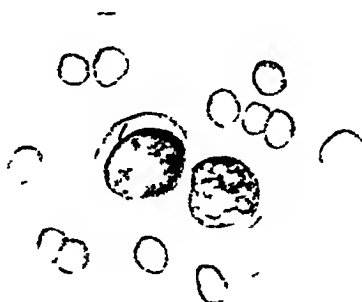


Fig. 181.—Two myelocytes, one showing an Auer body, and a few fine azure granules in the cytoplasm

bone-marrow (myeloid) series. He derives the erythrocytes and other leukocytes from this cell. The relation of this cell to the lymphocyte is not clear, but there is probably an intermediary

stage between the two types. The cell varies in size from 10 to 20 micra. It is characterized according to the Jenner-Giemsa stain by a fine, delicate, reticulated nucleus, containing two to six vacuolated areas (nucleoli) and by a small rim of cytoplasm. Discrete azure granules may be present diffusely in the cell or confined to the cytoplasm. Auer or rod-shaped bodies (Fig 181) may be present in such cells. The origin and nature of these bodies are not known, but the evidence seems to indicate that they are abnormal granules, according to staining qualities with polychrome stains and oxidase reaction. The rods are azure-like and give a positive reaction with alpha-naphthol and paraphenylenediamine.

The myeloblasts are more mature cells. The vacuoles of the myeloblasts are less distinct, and cytoplasm is often greater in amount. Granules are frequently present. Distinction between the myeloblast and some forms of lymphoblasts is not always easy on morphologic grounds alone. In such instances one has to depend upon the differential count and especially upon the oxidase reaction.

The Leukocytes of the Lymphoid Leukemias (Table IV) — With the newer methods of staining the number of acute lymphatic leukemias has become much smaller. The myelogenic and the myeloblastic leukemias have been confused with the lymphatic types, but the criteria mentioned above will be found extremely helpful in differentiating them. The presence of an acute lymphocytosis, especially if associated with large lymphocytes without the presence of amitotic lymphoblasts or Stern-

TABLE IV
LYMPHOID CELLS

Cell	Nucleus	Nucleoli	Cytoplasm	Granules	Oxidase reaction
Small lymph	Round	None	Small rim	None Azure	Negative
Large lymph	Round or slightly indented	None or 1 to 3	Moderate	None Azure	Negative
Lymphoblast of leukosarcomatosis (small or large)	Round and sharply indented	None	Small or moderate	None	Negative

berg's leukosarcoma cells is most often characteristic of a transitory infectious (?) lymphocytosis. The acute lymphatic leukemias of the small cell variety are more common than those of the large cell type.

The leukosarcoma cells (Fig 184) of Sternberg are lymphocytes undergoing amitotic division, as shown by the presence of sharp indentations of the nuclei and by the presence of two nuclei in one cell. The presence of a fair percentage of these cells in the smear indicates malignancy. A large mediastinal mass and large lymphoid tumors in various other regions are usually present. Histologically, the organs show a marked invasion by lymphoid cells. Leukosarcomatosis is not only confined to the lymphoid group. Acute myeloblastic leukemias may show the same malignant tendency and also the presence of a large number of myeloblasts exhibiting nuclear indentations (amitotic myeloblasts). Such leukemias are frequently associated with bone tumors, especially chloromata.

The Monocytic Leukemias—As indicated in Table I, such leukemias may occur. They are characterized by the presence of a large number of cells resembling the large mononuclears and transitionals of normal blood. The origin of these cells has long been a matter of controversy among hematologists and has not yet been settled. I have had the opportunity of studying 3 cases of leukemia in which these cells were predominant. Two of the cases were acute and one was chronic. Of the acute cases, one was associated with an increase of myeloblasts and myelocytes, and the other with an increase of small lymphocytes. The monocytic cells of the former showed finely reticulated round irregular nuclei characteristic of the monocytes, the cells in the latter case showed irregular nuclei with rather thick chromatin masses staining much lighter than the lymphocytes. Azure granules were present in both types of cell. The oxidase reaction was negative in both types of monocyte. In the first case the monocytes were probably altered myeloblasts and in the latter case altered lymphocytes.

The third case was an aleukemic monocytosis in a man aged thirty-four admitted to the medical service of Dr Brill, com-

plaining of progressive weakness and night-sweats for ten months. The physical examination showed that the patient had a moderate anemia, a very large spleen, and a palpable liver. The blood examination showed a persistent leukopenia (from 660 to 3000 white blood-cells)

One blood examination in this case gave the following interesting results

Hemoglobin	42 per cent	
Red blood-cells	2,240,000	
White blood-cells	3,000	
Blood-platelets	40,000	
	Per cent.	Absolute number
Polynuclears, neutrophilic	29	870
Lymphocytes	27	810
Monocytes	44	1320

Four months after admission the patient died. Histologic examination of the organs obtained at autopsy showed an apparently normal bone-marrow, marked congestion of the spleen, with dilated sinuses and lymphoid hypoplasia. The liver sections were remarkable. The interlobular regions and the capillaries between the liver columns contained large numbers of large mononuclear cells. It seemed as if the mononuclear cells were chiefly arranged peripherally in the liver sinuses, suggesting a derivation from the lining endothelium.

The monocytes are undoubtedly derived from myeloid, lymphoid, and endothelial cells. The latter are possibly indicated by their peculiar oxidase reaction, which is positive in the endothelial type, although somewhat modified in character. The granules in such cells are purplish or black, but not blue.

The Oxidase Reaction of the Cells in Leukemic Blood —
This reaction was introduced by Schultze in 1909 as a diagnostic method for the recognition of myeloid cells. He found that the polymorphonuclears, the myelocytes, and their forerunners show blue granules when stained with a mixture of alpha-naphthol and dimethylparaphenylendiamin, due to the presence in such cells of oxidizing ferments which synthesize

the two reagents into indophenol blue. This reaction is not present in lymphoid cells when performed according to his method. The reaction has not proved to be wholly satisfactory as a means of differentiation. According to the methods proposed, it has been found that the reaction is not conclusive evidence of the myeloid origin of blood-cells, as it is absent in ungranulated premature myeloid cells. Its action depends upon the presence of granules (neutrophilic, eosinophilic or azure granules, or Auer bodies) in mature and premature cells. The premature myeloid cells or altered myeloid cells (monocytes) in cases of leukemia show no oxidase reaction. The cells in such leukemias, according to the advocates of the oxidase reaction, would naturally be considered lymphoid in character. It seems that the morphology of the cells obtained by good polychromatic staining is the more important method of indicating the type of leukemia present in a given blood.

CASE I

H. M. Acute aleukemic myelosis (leukopenic myeloma).
Young girl. Age seventeen years. Admitted to service of Dr. A. Meyer, January 22, 1917, complaining of pain in chest and weakness.

The family history and past history were negative.

Present Illness—Onset one month before admission with pain in chest and precordium, also in lower abdomen. Fever, dyspnea, and weakness. Frequent vomiting. No cough. Marked night-sweats and chilly sensations. Lost 27 pounds in past month. Black-and-blue marks in skin, very profuse, all over body, at present very few remaining. Bleeding from gums. Pains in extremities. Marked constipation. Five days ago two teeth were extracted. Patient bleeding from gums since.

Physical Examination—General condition. Patient is acutely sick and appears markedly anemic.

Ears. Perforation in left drum membrane, with discharge.

Mastoids. Tip of left mastoid tender and slightly uneven.

Mouth. Breath foul. Marked necrosis of gums of lower

jaw on both sides Teeth in poor condition Tongue markedly coated

Face There is a marked tender swelling over right and left lower jaws and in submaxillary region, and slight induration

Lungs Anteriorly and posteriorly resonant No râles

Heart Not enlarged Blowing systolic murmur heard at apex and transmitted over precordium Action regular, sounds clear

Abdomen Upper border of liver at fifth interspace in mid-clavicular line Abdomen flat Spleen and kidneys not felt

Skin Shows bluish-red hemorrhagic areas over right side of neck, anterior aspect of left upper arm and outer aspect of right lower thigh There is a brownish pigmented area over left buttock There is a linear scar over inner aspect of left thigh

Lymph-nodes Posterior cervical and submaxillary nodes on both sides as well as axillary, inguinal, and femoral nodes palpable

Spine and joints Pain on moving temporomandibular articulation Spine negative Sternal tenderness present

January 23d Blood count

Hemoglobin	38 per cent
Red blood-cells	2,680,000
White blood cells	5,000
Polynuclears	19 per cent
Lymphocytes	78 "
Large mononuclears	2 "
Transitionals	1 "

Blood-pressure—105/70

January 25th Both optic nerves appear pale, but not atrophic, otherwise fundi are normal No hemorrhages Right ear shows no change Left ear-drum has large perforation in vertical meridian at periphery, through which are protruding several granulation masses—foul odor—evidently a long-standing process

The blood was reinvestigated somewhat more thoroughly with Pappenheim's blood stain and oxidase stain, with the following results

		Absolute number
Hemoglobin (Kuttner)	35 per cent	
Red blood-cells	1,720,000	
White blood cells	5,800	
Polynuclear neutrophils	17.0 per cent	966.0
Polynuclear basophils	0.3 "	17.4
Lymphocytes	28.7 "	1664.6
Myelocytes, neutrophils	6.3 "	365.4
Transitionals	1.0 "	58.0
Myeloblasts	20.7 "	1200.6
Myelocytes	26.0 "	1508.0

Red blood-cells show good shape and fair color. A large percentage of the myelocytes show the presence of Auer bodies.

About 65 per cent of the leukocytes showed a positive oxidase reaction.

	Per cent.	Graham oxidase reaction	Per cent	Pappenheim stain Oxidase reaction
Polynuclears and myelocytes	30	Many granules	24	Many granules
	4	Few granules		
Myeloblasts	23	Few granules	22	Few granules
Myelocytes	10	Few granules (Auer bodies)	11	Few granules (Auer bodies)
	3	No granules	6	No granules
Lymphocytes	30	No granules	31	No granules
			2	Small black granules
Transitionals			0.5	Few dull black granules
			0.5	No granules

January 26th No hemorrhagic areas seen in fundi.

January 27th Roentgen examination of the lower jaw shows on the right side the remaining roots of the second molar, and on the left side those of the last molar and probably of the bicuspid with small abscesses at the bases of these roots.

January 29th Hemorrhagic spots noted over right deltoid and left lower arm the result of hypodermic injection. A few purpuric spots noted over left lower back, left wrist, and inner aspect of left thigh. Small herpetiform area at right angle of mouth.

January 29th Blood count

Hemoglobin (Kuttner)	35 per cent
Red blood-cells	1,344,000
White blood-cells	4,800
Polynuclears	27 per cent
Small lymphocytes	34 "
Myelocytes	28 "
Myeloblasts	9 "
Basophilic myelocytes	2 "

Moderate poikilocytosis and anisocytosis Auer bodies still present in myelocytes

January 30th General condition growing progressively worse No fresh hemorrhagic areas seen Right side of face markedly swollen Patient complains of intense pain in right jaw Spleen not felt

February 1st Blood count

Hemoglobin (Kuttner)	20 per cent
Red blood cells	976,000
White blood cells	5,400
Polynuclears	20 per cent
Lymphocytes	34 "
Myelocytes (Auer bodies)	26 "
Myeloblasts	14 "
Basophilic myelocytes	5 "

February 1st Citrate transfusion given—400 c c Condition good at end of transfusion

February 2d Blood count

Hemoglobin (Kuttner)	29 per cent
Red blood-cells	1,336,000
White blood cells	2,260
Polynuclear neutrophils	25 per cent
Lymphocytes	34 "
Myelocytes (Auer bodies)	23 "
Myeloblasts	12 "
Transitionals	3 "
Myelocytes, basophilic	2 "
Normoblasts	1 "

February 3d Numerous new petechiæ on inner sides of both thighs General condition unchanged

February 6th Fresh hemorrhagic purpuric spots noted on inner sides of right and left legs

February 7th Hemoglobin 24 per cent before transfusion

February 7th Citrate transfusion—350 c c

February 9th Many crepitant and pleuritic râles heard over right side Fresh spots noted over left breast and left upper arm

February 10th Hemoglobin 20 per cent

February 10th A M Lung signs unchanged Fresh purpuric spots over left anterior chest

February 10th Patient died

Other laboratory reports

Blood Wassermann negative

Blood-culture negative

Urinalysis negative except for faint trace of albumin and occasional hyaline casts

Temperature varied daily from 99° to 105° F

Comment on Case—The first two blood counts done by members of the house staff with ordinary stains showed a leukopenia and lymphocytosis of 78 to 87 per cent The use of better stains showed that the lymphocytes were fewer than normal (absolute count 1600) and that myelocytes myeloblasts and myelogones were present and increased both relatively and absolutely In addition the myelogones showed the presence of Auer bodies in about 10 per cent of the cells The case ran the typical course of acute leukemia The hemorrhagic condition usually present in the ordinary types of acute leukemia, especially myeloblastic leukemia, was also a feature of this case Investigation of similar acute cases of this type of leukemia has shown that the hemorrhagic tendency is due to a diminution in the number of blood-platelets Blood-platelet counts ranging from 800 to 20 000 rarely higher have been the usual findings The tourniquet test that is constriction of the arm is always followed by a shower of petechial spots at the bend of the elbow within five minutes Blood-cultures performed on a series of

these cases have always proved negative, so that Sternberg's idea of an infectious origin cannot be substantiated. This type of leukemia appears to be due to a lesion of the hematopoietic organs induced by some unknown agent, producing a tremendous growth of premature myeloid cells not only in the bone-marrow but also in the liver, lymph-nodes, spleen, and kidneys.

CASE II

S T Chronic aleukemic myelosis (leukopenic myelemia)
Bence-Jones albumosuria

Housewife Age forty-nine years Admitted to service of
Dr Libman July 19, 1920 Discharged July 29, 1920

Chief Complaint—Pallor and weakness, dull pain in right
lower chest for two months

Family History—Negative

Previous History—Remembers no childhood diseases. No
other previous illnesses. Hysterectomy for uterine tumor eight
years ago at this hospital. No other operations. Menstrual
history normal. Menopause at time of hysterectomy. Married
twenty-three years. Husband living and well. Five children,
living and well. No miscarriages. Varicose veins of legs for
past twenty years. No gastro-intestinal symptoms. No urinary
symptoms except nocturia once or twice for eight to ten years.
No nervous system symptoms. Had dull aching pain in back
(right lower chest), especially on lying down, for eight months.

Present Illness—For past two months has been growing
progressively paler, and during the past five to six weeks even
somewhat yellow. Also has become progressively weaker,
making it difficult to stand for more than a few minutes at a
time. Has also had pain below right breast, dull in character
and radiating to right around to side of chest, not to shoulder or
to sternum. No nausea or vomiting. Pain is practically ab-
sent when patient wears corset, but is constant otherwise,
especially when in lying position. No fever. No chills. Occa-
sional flushing of face with sweating. No loss of weight.

Physical Examination—General condition. Rather obese
woman of forty-nine, slightly pale, and somewhat apathetic.

Mouth Lips somewhat pale Tongue somewhat smooth, clear, moist Tonsils cryptic

Heart Borders within normal limits Sounds at apex of poor muscular quality Low-pitched systolic blow in region of apex This is also heard from base to apex along the left margin of sternum Rate moderate, regular

Lungs Clear and resonant Sixth right rib in anterior axillary line exquisitely tender No nodules or irregularities felt

Abdomen Markedly pendulant

Spleen Felt 11 cm below left costal margin, firm, smooth, not tender

Liver Felt 10 cm below right costal margin No fluid wave or shifting dullness No other viscera or masses felt

Extremities Varicose veins of both lower extremities Few ecchymotic spots on right thigh and leg No weakness or paralysis Some pitting edema of both lower extremities

Spine Negative

Lymph-nodes Negative

Skin Brownish pigmentation of face No eruptions

July 20, 1920 Blood count

Hemoglobin	56 per cent
Red blood-cells	3,230,000
White blood-cells	3,900
Polynuclear neutrophils	44 per cent
Lymphocytes	51 "
Monocytes	3 "
Eosinophils	2 "
Index	9

July 20, 1920 Blood-pressure 130/65

July Marked poikilocytosis few stippled reds and occasional normoblasts

July 23, 1920 Blood count

Hemoglobin	47 per cent
Red blood-cells	3,030,000
White blood cells	5,900
Blood platelets	80,000

Differential (300 cells) Smear stained with Jenner-Giemsa

Polynuclear neutrophils	40.0 per cent
Polynuclear eosinophils	1.3 "
Myelocytes, neutrophilic	4.6 "
Myelocytes, eosinophils	0.3 "
Metamyelocytes	1.6 "
Myeloblasts	3.6 "
Lymphocytes	45.6 "
Monocytes	2.6 "

Red blood-cells show anisocytosis and poikilocytosis and polychromatophilia

Megaloblasts, 2 per cent Normoblasts, 4 per cent.

Diagnosis Leukopenic leukemia (myeloid type) or aleukemic myelosis

July 20, 1920 Blood Wassermann negative

July 20, 1920 Blood chemistry

Urea nitrogen	21.0 mg per 100 c c.
Incoagulable nitrogen	56.0 " "
Uric acid	3.5 " "
Creatinin	1.2 " "
Cholesterolin	0.200 per cent

July 22, 1920 Urine Bence-Jones bodies present Slightly turbid Acid reaction Albumin + Few hyaline casts

Temperature normal

Comment on Case—Here we are dealing with a woman forty-nine years of age with a nine months' history (to date January, 1921) of increasing pallor, weakness, large liver and spleen, secondary anemia, leukopenia, and premature myeloid cells. In addition, there is Bence-Jones albumose in the urine. All the facts point to some lesion in the bone-marrow. The blood examination ruled out pernicious anemia, Banti's disease, and splenic anemia. The differential diagnosis rests between malignant neoplasm and leukemia. A malignant neoplasm associated with multiple bone metastases can produce a myelophthisic or an osteosclerotic anemia, somewhat resembling the above blood-picture. The patient has not shown any cachexia or evidence of the presence of a primary new growth. We must

consider this case to be due to a hyperplasia of the myeloid tissue in the bone-marrow, spleen, and liver, manifesting itself by a slight increase of premature white blood-cells. The case is still under observation and will be reported later if new facts are brought to light.

CASE III

B R Acute aleukemic myelosis followed by acute myelogenous leukemia

Age twenty-four years. Admitted to service of Dr. Brill on June 24, 1916. Died on November 27, 1916.

Chief Complaint—Pain in abdomen, vomiting, and weakness.

Family history, personal history, and past history negative.

Present Illness—Began five months ago with pain and swelling in right foot, no redness. This lasted five days, followed by pain in knee and shoulder. At present has occasional recurrence of pain in joints. Three months ago began to have distress in epigastrium with feeling of fulness and vomiting. Vomiting has no relation to meals and occurs especially on exertion. Vomits less now because less is eaten. Later developed epigastric pain. Obstinate constipation. Weakness has gradually increased. Has been in bed two weeks. Six weeks ago had very severe sore throat.

Physical Examination (June 27, 1916)—General condition. Very pale. Color is sallow. Well nourished.

Mouth Tongue moist and slightly coated. Tonsils, especially left enlarged. Surfaces are irregular. Pharynx negative. Several small petechiæ on right half of palate. Several necrotic teeth. Upon gums both upper and lower are seen several small ulcers.

Skin Numerous small faded petechiæ upon the neck, right shoulder, and right upper extremity. Several ecchymotic spots on the right lower extremity.

Nodes Axillary and inguinal nodes palpable.

Chest Considerable sternal tenderness.

Lungs Negative.

Heart Not enlarged Action regular, slow Apex, soft systolic murmur, not transmitted Systolic murmur heard over pulmonic area and transmitted upward Venous hum present in neck

Abdomen Reflexes present Tympanitic No masses No rigidity No tenderness No free fluid Slight epigastric tenderness Cecum is spastic and tender

Liver and spleen not palpable

Extremities No edema Tenderness on percussion over the tibiae

June 29, 1916 Vomiting for a few days Few fine râles heard in the right interscapular region Temperature 99° to 101° F Fresh petechiae present on skin

July 3, 1916 Dulness and crepitant râles present in right apex posteriorly Gums are somewhat less swollen Petechiae present on right arm

July 4, 1916 An acute abscess is present in region of lower right second molar tooth

July 11, 1916 Anemia slowly progressing Pallor of conjunctivae is marked Petechiae are less distinct Lung signs unchanged Spleen not felt Right kidney palpable and tender

July 17, 1916 On the dorsum of the right hand there is a tender ecchymotic spot Hemoglobin has dropped from 50 to 30 per cent A direct transfusion (Unger method) of 500 c c was given

July 19, 1916 The day after the transfusion the temperature rose to 106° F, followed by a chill Lungs and throat clear Temperature today is 105° F No petechiae

August 2, 1916 Irregular fever (99° to 102° F) continues Bleeding from swollen gums A few fresh petechiae have appeared on palate, neck, and arms Systolic murmur over the whole precordium, loudest at pulmonic area

August 8, 1916 Alveolar abscess of right upper jaw Second and third right upper molars extracted

August 13, 1916 Anemia increasing Hemoglobin 18 per cent White cells unchanged (varying from 3600 to 5400) Relative lymphocytosis always present Few premature mye-

loid cells (myeloblasts, myelocytes) are also present Condition of teeth and gums is somewhat improved Cough for past week Lung signs unchanged Fresh petechiæ on skin

August 17, 1916 Direct transfusion (Unger method)—750 c.c.

August 19, 1916 Temperature still elevated (101° to 104° F). Fresh petechiæ on neck Patient looks better since the transfusion Hemoglobin increased to 35 per cent

August 31, 1916 Temperature has dropped steadily It is now usually below 101° F Coughs less Petechiæ still present

September 1, 1916 Hemoglobin 27 per cent

September 2 1916 Direct transfusion—750 c c

September 4 1916 Hemoglobin 46 per cent

September 12 1916 Few abscesses incised in right buttock and in coccygeal region

September 18, 1916 Following the drainage of the abscesses the temperature became normal Mouth infection well under control Hemoglobin and red blood-cells again falling

October 7, 1916 Temperature has been normal Today, for the first time, a petechia appeared in the right conjunctiva There are a few petechiæ about the neck and shoulders Lungs are clear Cardiac condition unchanged

October 15 1916 Today, for the first time, an increase of the white blood-cells to 15,000 and also an increase of premature myeloid cells was found

October 20, 1916 Temperature again rose to 101° F Hemoglobin now 14 per cent Gums are spongy and swollen Headache for several days

October 22, 1916 Direct transfusion (Unger method)—600 c c Hemoglobin 28 per cent after the transfusion

October 24 1916 Transfusion was followed by rise of temperature to 105° F and chill Many petechiæ have appeared about neck and arms The white blood-cell count and the premature myeloid cells gradually increasing (See blood counts and Figs. 182 183)

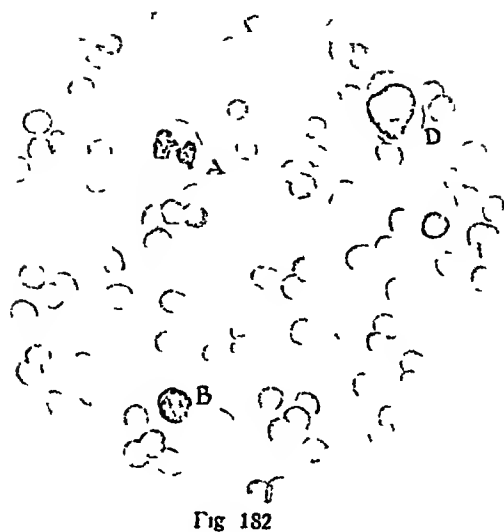


Fig 182

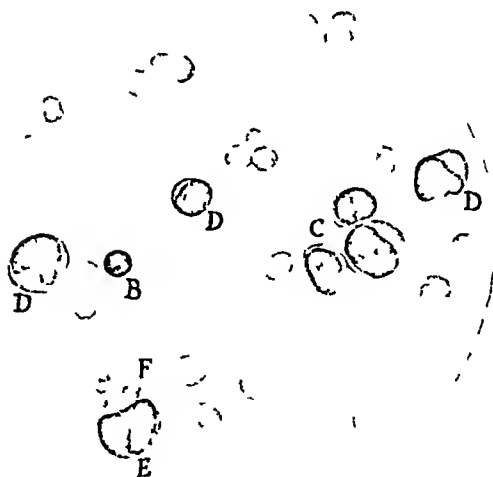


Fig 183

Figs 182, 183 —Fig 182, Blood smear of Case III in the aleukemic stage
A, Polynuclear neutrophil, *B*, lymphocyte, *D*, myeloblast Fig 183, Blood
 smear of Case III in the leukemic stage *B*, Lymphocyte, *C*, myelogones, *D*,
 myeloblasts, *E*, myeloblast undergoing amitotic division, *F*, small mass of
 cytoplasm with azure granules

October 30, 1916 Herpes of lips present The submaxillary glands have greatly increased in size Tonsils are large and clean Gums are swollen, but not infected

November 2, 1916 Painless, subcutaneous nodules, size of a bean, present over right internal malleolus and over right buttock

November 6, 1916 For six days temperature has been elevated The gums are greatly swollen The right side of the mouth is gangrenous The submaxillary nodes are greatly enlarged and tender The axillary and inguinal nodes are increasing in size Fresh petechiæ have appeared

November 11, 1916 Fever continues Gangrene of mouth is slowly increasing Spleen is not palpable Subcutaneous nodules in skin present

November 19, 1916 Patient has grown considerably worse today The color is more ashen (hemoglobin 9 per cent.) Respirations are rapid Patient fears imminent death

November 19, 1916 Direct transfusion (Unger method)—600 c c

November 19, 1916 Blood examination before transfusion

Hemoglobin	9 per cent
Red blood-cells	1,000,000
White blood-cells	151,000

November 21, 1916

Hemoglobin	23 per cent
Red blood-cells	1,664,000
White blood-cells	74,800

November 22, 1916 Patient is drowsy Gangrene of mouth extending

November 27, 1916 Patient became progressively weaker and died quite suddenly

LABORATORY REPORTS

BLOOD EXAMINATIONS

	June 24th	August 4th	August 10th	October 7th
Hemoglobin	50 per cent	30 per cent.	22 per cent.	19 per cent
Red blood-cells	1 520 000	1 600 000	1,840 000	1 552 000
White blood cells	3,900	5,400	4 000	6,600
Polynuclear neut	17 per cent	27 per cent	9 per cent	32 per cent
Myelocytes, neut			6 "	4 "
Myeloblasts		15 per cent	10 "	4 "
Myelocytes		7 "	4 "	2 "
Lymphocytes	83	51	69	58
Monocytes			2	
Normoblasts	None	4	2	
Megaloblasts	None	5	2	

	October 15th	October 20th	(After transfusion) October 27th	November 11th	(After transfusion) November 21st
Hemoglobin	16 per cent	14 per cent	24 per cent	14 per cent	23 per cent
Red blood-cells	1 104 000	1 050 000	1 600 000	1 300 000	1 664 000
White blood-cells	15 000	49 200	62 000	46 800	74 800
Polynuclear neut	12.0 per cent	17.5 per cent	7.0 per cent	7.5 per cent	4.0 per cent
Polynuclear eosin					0.5 "
Myelocytes, neut	7.0 "	7.0	1.7	5.0 "	17.5 "
Myelocytes eosin	0.5 "				2.5 "
Myelocytes, baso					0.5 "
Myeloblasts	6.5 "	14.5	5.3	6.5	18.5 "
Myelocytes	45.5 "	53.0	80.3	64.5	37.0 "
Lymphocytes	28.5 "	8.0	5.7	16.5	17.5 "
Monocytes					
Normoblasts	None	None	None	None	0.5
Megaloblasts	None	None	1	1	1.0

The red blood-cells showed moderate anisocytosis, poikilocytosis, and polychromatophila. No macrocytosis. Microcytes always present.

Blood chemistry Negative

Blood Wassermann Negative

Blood-cultures (2) Negative

Coagulation time, July 7, 1916 Six and a half minutes

Bleeding time, four and a half minutes

Urine Negative No urobilin present

Test-meals

	June 28th	July 2d
Mucus	Moderate	Moderate
Free hydrochloric acid	7	2
Total acidity	34	42
Blood	None	Traumatic
Lactic acid	Negative	Negative

Stools Negative for blood, ova, and parasites (many examinations)

Comment on Case—On admission the patient presented anemia, fever, cardiac murmur, petechiæ, and marked sternal tenderness. The two diagnoses were pernicious anemia and infective endocarditis. Two blood-cultures were negative. The color, pallor with pigmentation and the blood counts spoke against pernicious anemia. In his discussion of the case Dr Brill suggested the diagnosis of leukemia.

From the onset there was a lymphocytosis. Few premature myeloid cells (myeloblasts, myelocytes, and myelocytes) were constantly found. Some time later the total white blood-cell count rose to a high figure (over 100,000). There was also an enormous increase of the premature myeloid cells, especially myeloblasts (Fig 183). The liver and spleen were never enlarged. The enlargement of the submaxillary nodes was secondary to the mouth infection.

In this case there was a transition from the aleukemic (or leukopenic) to the leukemic type (Figs 182, 183).

CASE IV

J. R. Chronic lymphatic leukemia (Sternberg's leukosarcomatosis). Primary carcinoma of lung.

Age sixty-one years. Admitted to service of Dr N. E. Brill on February 24, 1920. Died on March 19, 1920.

Chief Complaint—Enlargement of glands in armpits and neck—four months. Cough and expectoration of blood—two months.

Family History—Negative.

Past History—Negative.

Present Illness—Began about four months ago, when patient noticed small lumps in both axillæ, which he thought were enlarged glands. These he discovered accidentally. Has had no pain in these lumps. About one month later he noticed similar lumps in the neck and also in the groin. None of these are painful or tender. About two months ago patient began to cough at night. This cough, according to description of patient,

is paroxysmal in character He brings up considerable sputum, which is streaked with blood Has also had well-marked hemoptysis during this period Has had occasional pain in the chest, sharp in character, and confined mainly to the left side During the past two months patient thinks that he has had no fever, but has had frequent night-sweats About one month ago noticed swelling of both legs This had intermittently increased and decreased at times Has lost some weight,

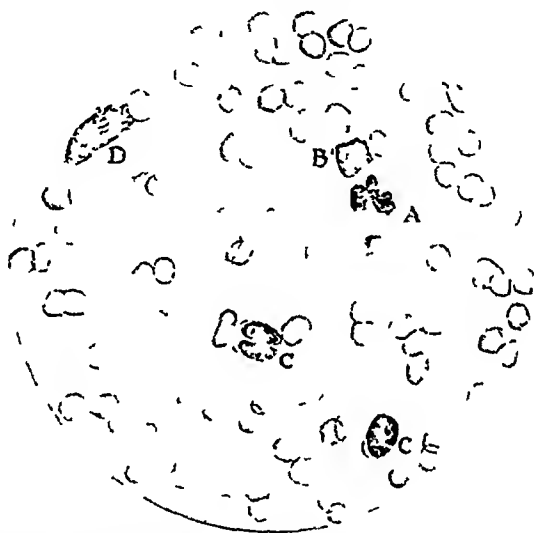


Fig 184 —Blood smear of Case IV A, Polynuclear neutrophil, B, lymphocyte, C, amitotic lymphoblasts, one containing two nuclei, D, Gumprecht "Schattenzelle"

doesn't know how much Feels weak No gastric disturbances Appetite fair Bowels fair No urinary disturbances No epistaxis No spots on skin No melena No sore throat

Physical Examination—General condition Well developed man, lying in bed, looks subacutely ill

Mouth Teeth in poor condition Tongue slightly coated and moist Tonsils not enlarged Pharynx slightly congested No bleeding gums

Neck Large lymph-nodes on both sides of neck and in

supraclavicular areas Some of the nodes are the size of almonds, others are smaller, not painful or tender

Lungs Clear and resonant throughout except for numerous sonorous râles scattered over both lungs

Heart Not enlarged Sounds regular, of good quality. No murmurs, thrills, or accentuations

Abdomen Slightly distended, tympanitic throughout Numerous small masses felt over entire abdomen A round mass, the size of a large orange, felt to the left of umbilicus A smaller mass felt to right of umbilicus These masses are not painful or tender A hard mass felt under left costal margin, not tender or painful (spleen?), felt on deep pressure and with patient lying on right side

Liver Upper border, fifth space Edge felt indefinitely three fingers below costal margin, firm edge Small nodules felt under liver

Kidneys not palpable.

Lymph-nodes Many nodes of various sizes, from a pea to an almond, on both sides of neck and in supraclavicular areas Many large axillary and inguinal nodes Not tender or painful

Skin Small fibroma behind left knee Numerous small telangiectases

February 25, 1920 Blood-pressure 125/74 (both arms)

February 25, 1920 Blood count

Hemoglobin	58 per cent	} Microcytes and macrocytes No normoblasts, no megaloblasts
Red blood-cells	3,200,000	
White blood-cells	49,800	
Polynuclear neutrophils	3 per cent	
Lymphocytes	97 "	

February 25, 1920 Sputum for tuberculosis negative

February 26, 1920 Blood count

Hemoglobin	60 per cent	
Red blood-cells	~ 200,000	
White blood-cells	100,000	
Blood platelets	60,000	
Polynuclear neutrophils	2 per cent	
Lymphocytes	95.5 "	(Small cells predominating)
Lymphoblasts	2.5 "	(Sternberg's leukosarcoma cells)

Slight anisocytosis No nucleated red blood-cells A few cells containing two nuclei were seen (Fig 184)

March 9, 1920 Signs of resolving pneumonia over right upper lobe Over right lower lobe posteriorly there is soft bronchial breathing, almost amphoric in quality, with few fine crepitant râles

March 9, 1920 Blood count

Hemoglobin	35 per cent
Red blood-cells	2,000,000
White blood cells	56,000
Polynuclear neutrophils	8 per cent
Polynuclear basophils	1 "
Lymphocytes	90 "
Myelocytes	1 "

Many degenerated white blood-cells Marked central pallor of reds No nucleated reds seen

March 18, 1920 Purpuric spots for past few days

March 20, 1920 Patient suddenly developed pulmonary edema and died

Urinalysis Negative for albumin, sugar, and casts

February 26, 1920 x-Ray examination of the chest shows a marked enlargement of the lymph-nodes at the roots of the lungs, especially on the right side, where they form dense masses There is, in addition, in the right upper lobe, in its axillary portion, a very dense pneumonic type of infiltration The right lower lobe is very much mottled, probably due to congestion (Fig 185)

Comment on Case —The patient was admitted to the hospital with a four months' history of progressive enlargement of the lymph-nodes, pain in chest, hemoptysis, and edema of the legs The blood examination in this case showed the presence of a lymphatic leukemia of small cell type, 21 per cent of the lymphocytes presented indentations of the nuclei, indicating cells undergoing amitotic division, and occasionally cells containing two nuclei were seen (Fig 184) From the presence of these cells it was suggested that this was a case of lymphosarcomatosis described by Sternberg

The cough, bloody expectoration, pain in the chest, and lung signs were interpreted as a pneumonia during life, but the autopsy showed that, in addition to a pneumonia and lymphoid infiltration of the right upper lobe, a carcinoma was present

Through the kindness of Dr Baehr I had the opportunity of studying smears and sections of the various organs obtained at the autopsy The lungs were bound down by adhesions In



Fig 185 —Case IV Enlargement of lymph-nodes at the roots of the lungs
Dense infiltration of right upper lobe

the middle of the upper lobe of the right lung there was an area 5 cm in diameter, which was solid dark red in appearance, and friable Small whitish nodules were scattered throughout the rest of the lobe The middle and lower right lobes appeared to be in the stage of gray hepatization The left lung was edematous The mediastinum contained a large mass of lymph-nodes The individual nodes were enlarged to about the size of a small egg On cut section they were pearly gray in color

The mesentery was the seat of a diffuse adenopathy. A great number of large discrete nodes were present in the region of the spleen, liver, and stomach.

The spleen and liver were not enlarged and did not show any gross lymphoid infiltration.

The microscopic examination of the various organs showed leukemic infiltration, especially in lungs, liver, kidneys, and



Fig 186—Case IV. Carcinoma of lung. Leukemic infiltration (leukosarcomatosis).

bone-marrow. The section of the hemorrhagic area of right lung was a mass of carcinomatous cells surrounded by fibrous tissue (Fig 186). The center of the tumor was occupied by a large hemorrhage. The rest of the right lobe showed an interstitial phenomena, areas of infiltration with small round cells (leukemic), and various areas of tumor tissue, consisting of large polyhedral cells with numerous mitoses and an alveolar arrangement. The picture was that of a medullary carcinoma.

Metastases were present in the bronchial and tracheobronchial lymph-nodes

The structure of the mediastinal and mesenteric lymph-nodes was entirely obscured, being replaced by small lymphocytes whose nuclei showed no mitotic figures. The capsule of the lymph-nodes was infiltrated with lymphocytes.

CASE V

M D B Acute monocytic leukemia

Age five years. Admitted to the service of Dr. Koplik on January 28, 1917, complaining chiefly of swellings on both sides of neck.

Family and past history irrelevant.

Present Illness—Began five weeks before admission with swelling on left side of neck that gradually increased, with the later development of similar swelling on right side of neck. Fever began day before admission. No vomiting. No convulsions. Cough for past two days. Marked constipation. No urinary disturbances or visual changes.

Physical Examination—Patient well nourished, appears bright.

Eyes Negative—no petechiae.

Mouth Tonsils moderately enlarged. Teeth fair, no gum changes.

Heart and lungs Negative.

Abdomen Liver felt two and a half fingers below the free border of ribs in midclavicular line.

Spleen Lower pole felt two fingers below costal margin in anterior axillary line.

Skin A few ecchymotic areas on both legs.

Nodes Numerous discrete nodes varying from size of pea to bean extending through anterior cervical, posterior cervical, and submaxillary groups on left side, right side, a few enlarged anterior cervical, posterior cervical and anterior maxillary nodes. Hard discrete axillary, and inguinal glands on both sides somewhat enlarged.

Two days after admission petechial spots developed all over

the skin, especially in the region around the umbilicus. The patient was removed from the hospital to a private sanitarium where he developed worse hemorrhages, delirium, and died. Unfortunately, no autopsy was obtained in this case.

Fever 100.2° to 103.4° F

Pulse 120-136

Respiration 32-40

Blood examination

Hemoglobin (Kuttner)	68 per cent
Red blood-cells	4,030,000
White blood cells	245,000

Differential (1000 cells counted)

	Per cent	Absolute number
Myeloid		
Polynuclear neutrophils	2.9	7,105
Polynuclear eosinophils	0.2	490
Polynuclear basophils	0.1	245
Myelocytes, neutrophilic	0.3	735
Myeloblasts	0.1	245
Myelocytes	0.1	245
Lymphoid		
Lymphocytes	8.1	19,845
Monocytes		
Large mononuclears	67.0	165,150
Transitionals	20.4	49,890
Nucleated reds		
Normoblasts	0.6	1,470
Megaloblasts (1 mitotic)	0.2	490

Pappenheim's oxidase reaction (500 cells counted)

Polynuclears, myelocytes, and myeloblasts	Positive, 4 per cent
Lymphocytes and monocytes	Negative, 96 per cent

The blood appeared interesting because of the extreme number of large mononuclears and transitionals present (Fig 187). The oxidase reaction was negative on repeated examinations, in spite of prolonged staining with alpha-naphthol and dimethyl-paraphenyldiamin. With the Jenner-Giemsa stain no definite blue nucleoli or vacuoles were present, but in a few cells thick-

ing of chromatin produced the appearance of small nucleoli. The granules in the cytoplasm were fine, reddish, and discrete.



Fig. 187.—Blood smear of Case V, showing a polymuclear neutrophil, a lymphocyte, and a group of monocytes.

No perinuclear pale zone was present as is the case in myeloblasts and lymphoblasts.

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